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NAVAL SCHOOL OF HEALTH SCIENCES
BETHESDA, MARYLAND 208894611

IN REPLY REFER TO:
NSHSBETHINST 6000.41B
OC MAY -2 2000

NSHS BETHESDA INSTRUCTION 6000.41B

From: Commanding Officer, Naval School of Health Sciences,
Bethesda

Subj: CLINICAL INVESTIGATION PROGRAM '(CIP)

Ref: (a) BUMEDINST 6000.12A
(b) 32 CFR Part 219
(c) NAVMEDCOMINST 6320.3B
(d) BUMEDINST 6710.69
(e) DoD Directive 3216.1 Use of Laboratory Animals in DoD Programs
(f) SECNAVINST 3900.39B
(g) OASD(HA) Memo Department of Defense (DoD) Guidance for Assurance of Compliance with the Federal Policy for the Protection of Human Subjects of 10 Jun 93 (NOTAL)

Encl: (1) Navy Clinical Investigation Program Guidebook

1 Purpose. To update implementation of the Clinical Investigation Program (CIP). This instruction contains detailed information about funding, preparation of clinical investigation protocol packages, review and approval processes, Clinical Investigation Department (CID) management reports, annual site visits and audits by the Naval School of Health Sciences (NSHS) Bethesda and formats used in the CIP. This issuance is a substantial revision and should be reviewed in its entirety.

2. Cancellation. NSHSBETHINST 6000.41A

3 Total Quality Leadership Principles. The Navy CIP supports the strategic plan, vision, and mission of the Navy Medical Department and NSHS, Bethesda. The CIP vision includes the following objectives:

- a. Improve the quality of health care for Navy, Marine Corps, and all other Department of Defense (DoD) beneficiaries.
- b. Generate an atmosphere of scientific inquiry.
- c. Promote an academic environment of high professional standing.

d Support accreditation of Graduate Medical Education programs.

4 Policy. NSHS Bethesda serves as Program Manager for clinical investigations conducted at Navy medical and dental treatment facilities (MTFs and DTFs), as directed by reference (a). The approval and conduct of human subjects research complies with the Federal Policy for the Protection of Human Subjects, as promulgated by reference (b). Additionally, Navy CIP policies are consistent with directives issued by the DoD, Secretary of the Navy (SECNAV), Bureau of Medicine and Surgery (BUMED), and with applicable regulations of other federal agencies (e.g., Food and Drug Administration (FDA) and Health and Human Services (HHS)). The following policies pertain:

a. Navy Department personnel are prohibited from accepting any compensation in addition to their salaries for the conduct of clinical investigations.

b. All clinical investigations are subject to military contingency requirements.

c. If an individual entitled to medical care and enrolled as a human subject loses his or her eligibility for care (e.g., the subject or subject's sponsor separates prior to retirement), and if the subject's continued participation in an investigation is likely to be beneficial to his or her medical well-being (e.g., enrollment in an oncology group protocol):

(1) Apply for Secretary of the Navy designee status for the subject if there is a Navy site in the subject's community where that study is active, or

(2) Attempt to transfer the subject to a nonmilitary facility in their community where that study is active.

d Activities may not compete with available commercial facilities in providing special services to agencies outside the federal government.

e. Data collected in a CIP study are the property of the Navy Department. Release of this data is not authorized without clearance by the proper approval authority. To be released, data must be for the benefit of medical science and not for the profit of private individuals. All manuscripts must have a statement within the text acknowledging that the interpretative findings and opinions are those of the author(s) and not of the Navy.

f. CIP investigators may not maintain custody of funds or other resources that support the program. Those resources must

remain under the cognizance of the comptroller at the principal investigator's medical or dental treatment facility (MTF or DTF), or by a third party specified in an approved resource sharing agreement.

g Every CIP project shall include an arrangement for treatment of any project-related injuries. Reference (a) specifies that only persons entitled to care in MTFs are eligible to participate as human subjects. When justified, waiver requests can be considered at BUMED, provided documented alternate arrangements exist for the treatment of project-related injuries. Those arrangements may be either the provision of Secretarial designation as DoD health care beneficiaries, or binding obligations for benefits equivalent to those available to DoD health care beneficiaries. Secretarial designee status may be granted to nonbeneficiary subjects in officially approved clinical research studies subject to the capabilities of the professional staff of the MTF and the availability of space and facilities, per reference (c).

h CIP investigators who plan collaborations with colleagues at other institutions must provide evidence of approval by the other activity. Institutional Animal Care and Use Committee (IACUC), and/or Committee for the Protection of Human Subjects (CPHS)/Institutional Review Board (IRB) approval should be documented, as applicable. A copy of an appropriately executed Letter of Intent, Memorandum of Understanding, Cooperative Research and Development Agreement or other resource sharing agreement, with local comptroller, Judge Advocate General, and Commander/Commanding Officer (CO) endorsement, is required.

i. Studies that may require submission of Navy prepared investigational new drug applications or new device exemption requests to the FDA will be reviewed and approved in accordance with references (a) and (d). Since Navy investigators are transient and enrolled subjects must be guaranteed follow-up treatment, the CO of the MTF or DTF at the intended site of performance, rather than the principal investigator of the proposed study, must be designated as the sponsor to the FDA.

j Navy Department personnel may not solicit gifts or contributions intended to benefit the Navy unless authorized by SECNAV. Grant applications must be signed by the CO of the MTF/DTF. Donors and grantors must be notified in writing that their gift/grant must be made to the Government on behalf of the MTF/DTF, and is not for the personal use of any individual.

k All laboratory animal research performed in DoD component facilities, or sponsored by the DoD or by its components, shall comply with reference (e). The BUMED Special Assistant for

Veterinary Medicine (MED-02E) requires that protocols proposing the use of non-human primates, cats, dogs or marine mammals must be submitted for review to MED-02E after local IACUC review is completed. If approved by MED-02E, the protocol may be implemented when approved by the CO of the local MTF/DTF. Other animal studies do not require prior approval from MED-02E. One copy of each locally approved animal protocol will be sent for information and reference to (1) MED-02E and (2) NSHS Bethesda, Code OC.

1. All retrovirology research (HIV-1, HIV-2, or HTLV-1) requires approval by the BUMED Human Immunodeficiency Virus (HIV) Program Division (MED-02H). To expedite review, study packages may be forwarded to MED-02H and to the CPHS/IRB concurrently. However, if either the CPHS/IRB or MED-02H require changes, written approval of the change must be obtained from the other party before routing to the MTF/DTF CO for final approval.

m. Per reference (a), the CO, NSHS Bethesda may delegate authority annually to the COs of MTFs/DTFs for local approval of all clinical investigations except for those involving dogs, cats, non-human primates, marine mammals, retrovirology research, and investigations requiring Assistant Secretary of the Navy (Research, Development and Acquisition) approval, per reference (f). Delegation of approval authority will be based on satisfactory annual inspection of the local program.

n. All CIP projects receive second level review at NSHS Bethesda for administrative completeness and compliance with relevant higher authority directives and guidance. Apparent discrepancies must be resolved to the satisfaction of the CO, NSHS Bethesda. Approved research must be conducted in accordance with all relevant Navy and federal policies, and be consistent with prevailing ethical guidelines (i.e., Belmont Report, Nuremberg Code, World Medical Association Declaration of Helsinki, etc.). For all research, involving human subjects, a medical monitor shall be appointed by name if either the IRB or the approval official determines the risk to be more than minimal. Additional guidance is provided in enclosure (1).

o. All Navy MTFs and DTFs must have an approved Assurance of Compliance with the Federal Policy for the Protection of Human Subjects on file before using human subjects in research. For the Navy CIP, NSHS Bethesda is responsible for approval of Assurance applications and for issuing a DoD Assurance number. References (b) and (g) pertain. Further guidance is provided in enclosure (1).

5 Summary. The opportunity to conduct clinical research has become an integral part of supporting excellence in health care

delivery to patients and providing quality education to the professional staff. Enclosure (1) is an essential reference for all Medical Department personnel involved with implementing, administering and conducting clinical investigations at Naval MTFs and DTFs. It should be widely distributed. The staff at local CIDs and at NSHS Bethesda (Code OC) are available to provide assistance and additional guidance to all CIP participants.


D. A. WYNKOOP

Distribution:

List I

BUMED WASHINGTON DC (MED 02H)

BUMED WASHINGTON DC (MED 02E)

BUMED WASHINGTON DC (MED 05B)

All MTFs and DTFs

NAVY CLINICAL INVESTIGATION PROGRAM GUIDEBOOK

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1. INTRODUCTION

a. This handbook specifies detailed policies, procedures and formats required or recommended by the Director, Clinical Investigation Program (CIP), Naval School of Health Sciences (NSHS) Bethesda Code OC. Higher authority directives are referenced in context, but their detailed guidance is not reiterated. Readers should note that this handbook is extensively referenced, and that the reference list (page xlv) differs from the reference list of the parent instruction. In cases of discrepancy among directives from different echelons or offices, the most restrictive policy applies, regardless of date of promulgation, unless explicit written waiver is requested via the chain of command, and received from the office responsible for that policy. APPENDIX 1 provides a consolidated list of acronyms used in this handbook.

b. At each activity where clinical investigations (CIs) are performed, clinical investigation departments (CIDs) and/or their institutional review committee chairs, or in the case of Satellite Facilities (SFs), research coordinators or directors are expected to have convenient local access to a complete set of current relevant directives (either in hard copy or via reliable electronic information systems), both for the benefit of their own staff and for investigators.

c. All comments pertaining to this handbook are welcomed, and should be communicated to NSHS Bethesda, Code OC.

2 ORGANIZATION AND FUNCTION. For the Department of the Navy, levels of responsibility for oversight and management of the CIP have been established by references (a) through (c). NSHS Bethesda serves as the central program management office to implement all policies regulating the Navy CIP.

a. Naval School of Health Sciences, Bethesda (NSHS)

(1) Commanding Officer (CO)

(a) Holds final approval authority for almost all CIP human use protocols with the exception of studies defined by reference (b) that require approval by the Assistant Secretary of the Navy (Research, Development and Acquisition). When authorized by the Navy Bureau of Medicine and Surgery (BUMED), CO, NSHS Bethesda takes final action on retrovirology protocol recommendations from the HIV Program Division Director (MED-02H). With cause, CO, NSHS Bethesda may require immediate

suspension or termination of a study, withdraw delegated local approval authority, or withdraw acceptance of an Assurance Agreement from a CIE? site.

(b) Advises BUMED on all budget and policy issues pertaining to the CIP, and administers centrally funded aspects of the program (i.e., CIP investigator travel).

(c) Delegates protocol approval authority to COs of Navy medical treatment facilities (MTFs) with CIDs. Delegated local approval authority is based upon successful completion of annual inspections that include an on-site audit of locally managed CIP records and files, and interviews with selected MTF staff. Delegated local approval authority is also based on the on-going assessment of institutional review organization (IRO) compliance with the Federal Policy for the Protection of Human Subjects, as monitored during second level review. Inspections are graded satisfactory or unsatisfactory.

(d) Acts as liaison and point of contact for official Navy CIP communication with higher authorities and with parties outside the DoD, including federal agencies and the Henry M. Jackson Foundation for the Advancement of Military Medicine (HMJFAMM).

(2) Clinical Investigation Program Director (Code OC)

(a) Implements policy issued by the CO, NSHS.

(b) Maintains the official central record system for the Navy CIP.

(c) Coordinates and conducts annual on-site inspections of CIDs, identifies areas of noncompliance and recommends appropriate corrective actions and policy changes.

(d) Reviews study files, reports, requests for funded travel, and other incoming communications to NSHS Bethesda (Code OC). This review provides an opportunity to perform on-going quality assurance assessment for compliance with policy and directives. CIP sites may receive requests for explanation or additional documentation, as warranted.

(e) Prepares annual program reports for submission to the Assistant Secretary of Defense (Health Affairs) (ASD(HA)), and to other higher authorities as directed.

(f) Coordinates an on-going education program for CIP personnel. During annual visits to Navy medical facilities with CIDs, members of the inspection team provide situational on-site training and guidance for implementation of instructions and policies. In addition, the CIP office forwards all relevant regulatory and training information it receives to MTFs and dental treatment facilities (DTFs) with an active or pending Assurance agreement for compliance with the federal policy for the protection of human subjects in research. Each MTF and DTF with an Assurance agreement will provide NSHS Bethesda (Code OC) the e-mail address and telefax numbers of their designated point(s) of contact to facilitate on-going communications.

(g) Develops, maintains and distributes NSHS Bethesda directives and publications which detail program policies, and which provide formats and outlines for CIP documentation.

(h) Supports the acquisition and distribution of higher authority CIP directives to active CIP sites.

(i) Sponsors periodic workshops to update and train CIP personnel. Workshops may be held during the annual tri-service Clinical Investigation Postgraduate Short Course. These workshops may include lectures as well as discussions on topics relevant to the CIP. Suggestions for workshop topics and agenda items are welcome at any time, and should be provided to NSHS Bethesda (Code OC).

b Navy Medical Activities with CIDs. The CO of a Navy medical department activity with an established CID and IRO that is in compliance with reference (d) can receive delegated approval authority from the CO, NSHS, based upon an annual inspection of the CID. The activity's CO, review committees, and CID must ensure compliance with all applicable Federal, DoD and Navy policies pertaining to the CIP.

(1) CO

(a) Autonomously approves (if delegated the authority by CO, NSHS Bethesda) CI proposals which **DO NOT** involve retroviruses, cats, dogs, non-human primates or marine mammals. Final local approval of research protocols with any of the above special criteria is contingent on written notification of approval by either the BUMED HIV Program Division (MED-02H) or the BUMED Special Assistant for Veterinary Medicine (MED-02E) as appropriate. In addition, local approval authority does not

pertain to special categories of studies that require Assistant Secretary of the Navy (Research, Development and Acquisition) approval, per reference (b). In no case can the CO approve a study that has not received a favorable recommendation from the relevant local advisory board(s) (see below) and prior approval from a higher authority reviewer (if required). Study packages should not be forwarded to higher authority for review and/or approval unless they can be provided with a favorable endorsement from the forwarding CO.

(b) Develops local policy and establishes an administrative process for reviewing, investigating, evaluating, reporting and resolving allegations of scientific misconduct in clinical research.

(c) Implements procedures intended to preclude abandonment of investigations in progress when the principal investigator detaches from the command.

(d) Promulgates local policies that establish, staff, and adequately support a CID and the following advisory boards:

1. Institutional Review Organization (IRO).

2. Radiation Safety Committee (RSC).

3 Institutional Animal Care and Use Committee (IACUC) (if animals are to be used on-site).

(e) Provides sufficient resources to enable the accomplishment of CIs that are proportionate to the abilities of the professional staff.

(f) Establishes a system for tracking and managing all the fiscal and other tangible resources allocated and expended for the conduct of CIs each fiscal year, regardless of source. The system should enable study-specific and consolidated reporting to higher authority by resource category and minimize the possibility of conflict of interest by the custodian(s) of those resources.

(2) Clinical Investigation Department (CID). CIDs serve as local CIP program manager and liaison for individual investigators and are the local source of subject matter expertise for administrative and technical support issues pertaining to CIs. They provide administrative and clerical

support to the IRO, but in no case shall they refuse to forward a proposal to the IRO for reasons of questionable scientific and/or ethical acceptability. The head of each CID shall be appointed by name and be responsible to the CO of the Naval MTF/DTF as directly as is feasible, but in no case, via more than two intermediate levels in the chain of command. In general, if a MTF/DTF has sufficient CI activity to warrant the establishment of a CID and supporting advisory boards, the work load and responsibility assigned to the CID head justifies the position being a full time billet versus a collateral duty. cos must ensure that CID heads do not assume excessive collateral duties to the detriment of the CID.

The Head, CID:

(a) Helps the CO enforce regulations and policies as they relate to CIP.

(b) Reviews CI proposals for administrative completeness and accuracy prior to submission to the IRO.

(c) Promotes, manages and supports CIP activities within allocated resources to include: coordinating all routing of clinical research proposals, ensuring timely reviews at all required advisory boards, maintaining properly secured files on all CIP research (with identifiers on all subjects enrolled in each study), maintaining advisory board reports, and serving as a resource to assist investigators to develop, prepare, and submit CI proposals.

(d) Promptly forwards all adverse event reports to the appropriate advisory board chair.

(e) Prepares CIP reports for submission to higher authority as directed.

(3) Advisory Boards. The membership of each advisory board and their voting status on that board must be carefully considered to preclude a conflict of interest or opportunity for inappropriate influence on the activities of that board. The CID staff normally provides administrative and clerical support and serves as recorder to the IRO boards, but they are prohibited from participating in board activities as either chairperson or vice-chairperson.

(a) Institutional Review Organization (IRO). The IRO can be configured as a unified Institutional Review Board

(IRB), as an IRB with separate scientific review and protection of human subjects subcommittees, or as two entirely separate committees, i.e., scientific review committee (SRC), and committee for the protection of human subjects (CPHS). The CO of the local MTF/DTF will appoint by name, the regular and any alternate members of the IRO. More than one SRC, CPHS, or IRB may be established, if preferred. Prerequisites for membership, and designation of assigned responsibilities will be consistent with references (b) and (c), and as defined below:

1. Membership .

a. Each board, committee or subcommittee will include a chair who is not a staff member of the CID. The chair will vote only to break tie votes by the other voting members. Non-voting members may be appointed as desired.

b. A quorum is defined as a majority of regular **voting** members (or voting members' designated alternates), and must include at least one voting medical corps officer and one voting member whose primary concerns are in non-scientific areas. However, the chair is not to be counted towards the quorum. In the absence of the chair, the meeting will be lead either by a previously appointed vice chair, or by an acting chair, selected by consensus of all regular and alternate members attending that meeting. The substitute chair should be a voting member or voting member's designated alternate, in order to qualify to break tie votes by the other voting members of the quorum. Otherwise, the substitute chair will not vote while acting as chair, and will not qualify to fill the quorum for that meeting.

c. Alternates should be appointed, especially for voting members, to maximize the availability of a quorum for each meeting. Alternate voting members are to substitute for specific regular members and cannot contribute to a quorum or vote if their counterpart is voting on the same motion at that quorum. Their attendance at part or all of any meeting with their counterpart is appropriate but not mandatory if the regular member anticipates a conflict of interest that will require recusal from any vote. Local policies should be established to ensure that alternate members receive relevant read-ahead materials in sufficient time to become familiar with agenda items prior to their participation in a vote.

2. Scientific Merit. The scientific merit of each proposal must be evaluated. For CIs, there is no

justification to assume any risk to human or animal subjects, or to spend any resources, unless the proposed investigation meets acceptable standards of scientific quality. The following items, at a minimum, must be considered by the SRC or IRB:

a. Background, aims and hypothesis, including adequate literature search, documented in context in the text of the proposal. Background searches should be sufficiently extensive to provide reasonable expectation of detecting prior accomplishment of the proposed study.

b. Study design, specific and special procedures, and proposed time schedule, including time to prepare one conference presentation and/or manuscript for submission for publication.

c. Qualifications of the principal and assistant investigators.

d. Resources (including budget) and facilities required.

e. Population of subjects.

f. Precautions to minimize procedural risks.

g. Statistical analysis based on the study design and the number of proposed subjects.

3 Human Use Issues. The IRB or CPHS must consider all comments and recommendations from the RSC (if applicable) in addition to the scientific review. The following specific human use issues should be assessed at a minimum, per references (a) through (g):

a. Appropriateness of the subject populations (i.e., inclusion/exclusion criteria, need for special populations, such as pediatric, female, or active duty subjects).

b. Risk-to-benefit ratio.

c. Compliance with the Investigational Drug Clinical Information brochure (IDCI) if using investigational drugs or biologics, with the manufacturer's brochure if using investigational devices, and compatibility with the command's

responsibilities and liabilities if the proposal requires local sponsorship of investigational agents.

d Ensuring subject privacy with regard to storage of identifiers and data.

e. Reviewing subject recruitment media and informed consent forms and procedures to ensure that (1) potential subjects are not contacted or their private identifiable data are not retrieved by misusing clinical care records, (2) there is no coercion, (3) subjects are likely to be able to comprehend all pertinent information, and (4) all elements of informed consent are appropriately addressed.

f Investigator plans for data monitoring, medical monitoring (if greater than minimal risk), anticipated need for future protocol amendment, and compliance with all relevant reporting requirements.

g Appropriate assignment of interval for continuing review of each non-exempt (see immediately below) protocol that is recommended for approval.

4. Expedited and/or Exempt Research. Certain categories of investigations may present either negligible or no apparent risk to subjects. In those cases, reference (d) authorizes reduced institutional oversight. However, the decision of whether a study qualifies for expedited review or is exempt from review must not be left to investigator or department head discretion. Local policies should ensure that potential investigators are informed of the IRO's responsibility for determining review requirements. When a study has been determined to qualify for either expedited review or to be exempt from the requirements for review, the protocol document or relevant IRO minutes should cite the specific regulatory criterion that pertains.

a. **Expedited** initial and continuing review procedures are authorized by reference (d) for certain categories of research involving no more than minimal risk, and for minor changes in previously approved research during the period for which approval has been authorized. The review may be carried out by the IRB or CPHS chair or by one or more experienced reviewers designated by the chair from among IRB or CPHS voting members. The categories of research that qualify for expedited review are specified in a list prepared by the Secretary, Department of Health and Human Services, and

published periodically in the Federal Register. A copy of the most up to date list is available from OPRR (the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892). At this time, the current list is also available at: <http://www.grants.nih.gov/grants/oprr/humansubjects/expedited98.htm> on the World Wide Web.

b. Certain categories of research involving human subjects may be **exempt** from reference (d). Section 219.101(b) of reference (d) specifies those categories.

c. The use of expedited and exempted categories is not mandatory. Local activities may elect to require full review for either or both categories of research. However, the following categories of studies must receive full review:

- (1) Third party consent.
- (2) Animal models.
- (3) Studies requiring investigational new drug or new device applications to the FDA.
- (4) Retroviral agents.
- (5) Assistant Secretary of the Navy (Research, Development & Acquisition) approval.

(b) Institutional Animal Care & Use Committee (IACUC). In MTFs/DTFs using animals for research, the CO will establish an IACUC of at least five members that meets the requirements of reference (h). The CO is ultimately responsible for compliance with references (h) through (1). The IACUC has two major functions:

1. Review all animal use proposals for scientific rationale, number of animals required, experimental design, types of anesthesia, analgesia and euthanasia, and adequacy of personnel, using, at a minimum, references (h) through (1) for guidance, and determine acceptability.

2. Conduct semiannual inspections of the research activity's animal facilities, including both the physical plant and the facility's program for humane care and use of animals. The IACUC will prepare and submit a written

report to the CO of the activity, via the CID Director. This report must specify major and minor deficiencies and establish a reasonable timeline for deficiency correction. The IACUC must monitor to see that the timeline is met, or report through channels that it has not been met, per reference (j).

(c) Radiation Safety Committee (RSC). The CO will establish a RSC if using, or intending to use sources of ionizing, acoustic (including but not limited to ultrasonic), or electromagnetic (including but not limited to ultraviolet, visible, or infrared) radiation in a CIP investigation. However, if the subjects' only exposure to radiation is from the portion of a technical approach that provides standard of care diagnosis and/or treatment of a medical condition, if the proposal qualifies for expedited review, or if the **device** emitting the radiation meets the definition of an FDA non-significant risk device, RSC review is not required. The RSC will ensure that all the CIP proposals it evaluates discuss radiation safety precautions per references (m) and (n) and that if applicable, principal and associate investigators are adequately trained to recognize and treat overexposures and to safely handle the sources of radiation specified in the proposal, including the disposal of any excess or contaminated materials. For human use protocols, the committee shall critique the proposal's risk/benefit analysis that justifies the risk of investigational exposure to the radiation source(s). CO's are encouraged to expand the responsibilities (and membership, if appropriate) of an existing committee that may have been established solely to review the safe use of ionizing radiation in the clinical setting rather than establish a separate RSC to support the CIP.

C. Satellite Facilities (SFs). For the purpose of this instruction, all Navy medical and dental facilities that do not have a CID are referred to as satellite facilities. APPENDIX 2 designates the geographic areas that each CID will support.

(1) CO. Although CIP proposals must be reviewed and approved by another MTF's IRO, the SF's CO remains responsible for certifying investigations conducted at his/her command. A Research Coordinator or Director should be appointed to assist in administering some or all of the satellite CO's responsibilities enumerated below:

(a) Ensure that all personnel who are involved in the CIP are adequately trained and competent to perform their

duties ethically, professionally, and in accordance with all applicable regulations.

(b) Develop local policy and establish an administrative process for reviewing, investigating, evaluating, reporting and resolving allegations of scientific misconduct in clinical research.

(c) Implement procedures intended to preclude abandonment of investigations in progress when the principal investigator detaches from the command. .

(d) Obtain on-site review of all protocols, consistent with local professional resources, to facilitate either endorsement and forwarding to the designated CID or return to the principal investigator. The composition of the local reviewing board is not expected to conform to the IRB requirements of reference (d). However, local IACUC and RSC review must be accomplished for applicable protocols (see above). If an activity does not have sufficient on-site expertise to appropriately staff a IACUC or RSC, it should not support protocols requiring animal use or radiation unless there are suitable support agreements with collaborating activities that can provide that expertise. All local evaluations should be forwarded to the supporting CID along with the proposal.

(e) Provide sufficient resources to enable the accomplishment of CIs that are proportionate to the abilities of the professional staff. Resources include support staff, equipment, drugs, and other consumable supplies, as applicable. If the command is unable to provide these resources, help the investigator find outside sources of support. (It is not the responsibility of the CIDs or of NSHS, Bethesda to fund CI projects at SFs.)

(f) Provide sufficient resources to enable appropriate communications and on-site contact (when required) between the principal investigator (PI) and the supporting CID/IRO during initial review, at all continuing reviews required by reference (d), and between reviews, if necessary.

(2) Support from the SF's CID and the CID's Command

(a) Upon request from satellite MTFs in their area of responsibility, assist in developing Assurance applications to NSHS Bethesda.

(b) Serve as a resource to assist SF investigators develop, prepare, and submit CIP proposals, requests for travel funds, and required reports.

(c) Provide IRO review of SF CIP protocols for scientific merit and human use considerations.

(d) Approve qualifying proposals within the limits of delegated authority. It is important to note that the Commander/CO of the supporting MTF with NSHS Bethesda delegated approval authority is responsible for the approval, but not the conduct of a SF study; certification is the responsibility of the CO of the activity where the PI is assigned. (Permission to conduct any CI may be withdrawn by any endorsing or approving authority in the chain of command if warranted.) Upon approval, a letter will be sent to the CO of the SF stating that:

1. The IRO reviewed the protocol and recommended that it be approved.

2 Human use issues were reviewed and found acceptable (if applicable to that specific protocol).

3 Approval is granted to begin the study (pending final local certification), along with notification of the date of the first continuing review.

4. A copy of the approved study package will be provided to NSHS, Bethesda.

(e) Develop a system for the timely preparation and submission of letters to the SF's CO that provide reminders of deadlines for continuing reviews and all required reports.

(f) Enter all approved protocols originating at SFs into the CID's database for monitoring and recording purposes. The database records should be coded (and the paper records filed) to enable easy retrieval by site.

(3) Proposal Administrative Procedures at SFs

(a) The study package must be reviewed by the SF's local evaluation board(s) for written recommendation to their CO for possible favorable endorsement. All packages, whether new proposals, modifications required by the supporting CID's IRO,

or investigator initiated amendments, must be favorably endorsed by the CO prior to submission to the supporting CID.

(b) If favorably reviewed, the CO of the SF may favorably endorse the protocol and forward it to the supporting CID. (As noted above, the CID will review the protocol for completeness and assist the PI, if necessary, with the presentation to the IRO.)

(c) If the PI is not able to visit the IRO, any convenient medium of communication can be used to resolve problematic issues, as long as the substance and resolution of those issues is documented via mail, telefax, or e-mail.

(d) Appropriate administrative data for all approved protocols will be entered into a local database at the SF to monitor the submission of periodic review reports, track continuing review dates, and to record changes in investigators.

(e) The SF will promptly submit to the supporting CID, all required reports and forms that document the conduct of CIs, including periodic review reports (with patient identifiers), continuing review documentation, protocol changes, and adverse event reports.

d Principal Investigator (PI). The PI may be any federal employee (uniformed or civilian), in a training or staff position, at the Navy MTF or DTF where the research is to be performed. The PI is the individual who is primarily responsible for the documentation and conduct of a research project. Specifically, the PI is responsible for the following:

(1) A properly prepared, printed proposal, in the appropriate format, with all the data elements that are required by this guidebook and other applicable instructions and regulations.

(2) Ethically managed and performed research, per this guidebook and other applicable regulations. All investigators approved to conduct research within the Navy CIP are required to read, at a minimum, *Standards of Conduct*, reference (o), and if the research involves the use of human subjects, the Belmont Report, and *Protection of Human Subjects*, reference (b). Each investigator must agree in writing to abide by the provisions of those references during the conduct of a Navy CIP research protocol. For greater than minimal risk studies, no subjects will be enrolled until requisite resources have been received to

accomplish either the entire study or the first fiscal year's period of performance (in the case of studies that are anticipated to require more than one fiscal year to complete).

(3) Information to the CID for:

(a) Continuing review, if the research involves non-exempted categories of human use.

(b) Reports, including change of investigators, amendments, requests for extensions and/or increased enrollments, periodic review reports, and reports of adverse events during the conduct of a CI.

(4) Maintaining the following documents and records:

(a) Approval letters.

(b) Correspondence to and from the IRO and CID.

(c) Patient identifier codes. Patient names and social security numbers (SSNs) or other easily traceable personal identifiers must NOT be included on data sheets. Appropriate measures must be taken to safeguard the confidentiality of all identifying data.

(d) Informed Consent File (if appropriate), containing a copy of all IRB/CPHS approved versions of information for subjects and consent forms as well as the original dated, signed and witnessed (with witness' dated signature) consent form for each subject enrolled in the study.

(5) Ensuring that applicable security measures are taken to provide privacy and anonymity to research subjects and to project documents.

(6) Making a timely, good faith effort to prepare and submit at least one presentation or manuscript describing the research findings to a reputable scientific meeting or publication.

3. ESSENTIAL ELEMENTS FOR A CIP AT MTFS WITH A CID

a. Departmental Research Coordinator. Each Department with investigators participating in clinical research should appoint an individual who is interested in research and preferably, in

research training. That individual will promote research within their department, maintain a working knowledge of the regulations related to clinical research, assist colleagues with writing protocols, interface with the CID and other key IRO personnel and coordinate research training for the department, as appropriate.

b. Institutional Review Organization. The IRO must not only be constituted in accordance with all applicable regulations, but its membership must have the background, training and commitment to support the institution's Assurance Agreement. The IRO may be a single IRB or a coordinated SRC and CPHS. The chair(s) must possess sufficient expertise in research, knowledge of the applicable regulations and skill in human relations to negotiate and resolve conflicts that commonly involve research ethics, protection of subjects, and the desires of investigators.

c. Clinical Investigation Department. The CID must meet the following minimum functional requirements. Resources and services can be provided by staff assigned to the CID or by alternate arrangements, provided that they are reliably and conveniently accessible to the IRO and to investigators.

(1) Scientific methodology/statistical analysis.

(2) Research administration.

(3) Office automation for the system of records required by reference (d) and other higher authority to enable timely accomplishment of the CID mission, including reporting requirements. Master files may be established for IRO minutes and for investigator C.V.s, provided that the individual study files contain properly cross referenced annotations to the appropriately designated master copy, and that a second site archiving system is established to permit file restoration in the event of severe damage or loss of the primary master file. C.V.s must be marked with the month and year of preparation, and older versions retained.

(4) Fiscal and legal support for the preparation of collaborative support agreements, letters of intent, and other official documents that may be required to obtain and account for extramural resources.

(5) Supply and procurement support to obtain research related supplies, equipment, services, contracts, and leases.

(6) Editorial review and clearance of draft manuscripts, posters, abstracts, etc.

(7) Illustration and graphics support (optional, but highly desirable).

(8) Laboratory animal care and use (optional, but highly desirable).

d. Training Requirements. Effective initial and on-going education and training of departmental Research Coordinators, IRO members and CID staff is critical to maintain the expertise and integrity of the CIP. Relevant topics must include, at a minimum, ethics in research, protection of human subjects, animal rights (if relevant to that site), scientific misconduct, and the research review process. Training requirements can be met by:

(1) Review of pertinent literature at journal clubs or peer group discussions during IRB/CPHS/SRC meetings.

(2) Presentation of classes or short courses, including the *use of pre-packaged instructional material.

(3) Attendance at meetings such as the Army Medical Department's Clinical Investigation Postgraduate Short Course, NSHS sponsored workshops, FDA or NIH workshops, or meetings sponsored by professional societies such as Public Responsibility in Medicine and Research or the Applied Research Ethics National Association.

(4) On-going review of e-mail messages submitted to the Medical College of Wisconsin's IRB Discussion Forum, available for free at: <http://www.mcwirb.org/>.

4. FUNDING OF NAVY CIP INVESTIGATIONS. Each MTF/DTF is responsible for supporting the performance of the CIs at their activity (i.e., for protocol expense elements enumerated in paragraph 7. of APPENDIX 3). If an external source of support has been identified, COs will be guided by references (o) through (r). **CIDs do not fund studies at SFs, and NSHS Bethesda does not fund studies at any MTF/DTF.**

a. General Guidelines

(1) A defined, designated Command budget for CIP research provides a much more conducive research climate than a Command policy that requires reprogramming from other budgeted funds each time a meritorious proposal is approved.

(2) To facilitate consolidated reporting, maximize accountability, and minimize any appearance of conflict of interest, centralized management of CI funds by a CID or Research Director is usually preferable to distributed management of research funds by each PI's department head (or similar arrangement).

(3) The appropriate amount of Navy funds to be designated for each study will be determined by the CID head, with recommendations from the SRC or IRB.

(4) The budget for each approved CI must be monitored by the comptroller. At least one unique Job Order Number (JON) per study should be established by the comptroller and the CID head or Research Director for all studies requiring the expenditure of Navy funds (other than NSHS Bethesda sponsored travel).

b Eligibility for Funding. After a protocol is approved by a Navy official with delegated approval authority, it is eligible for funding to support the conduct of the study, publication costs, and for invited travel to conferences to present findings. Navy officers entering full time off-site training programs can continue to be eligible for Navy support of an approved study at their parent command if they remain actively involved with that CIP project.

c. Equipment Costing >\$100,000.00. Procurement of high cost equipment must be accomplished via the Naval Medical Logistics Command, Fort Detrick, MD. CID heads and Research Directors are advised to consult their local comptroller for detailed guidance on the preparation of appropriate paperwork.

d Travel to Present CIP Research. NSHS Bethesda manages a modest budget for travel to support invited presentations of CIP studies. Funded travel is a reward for research well done. Funds are provided (when available at NSHS Bethesda) on an individual request basis. However, non-availability of travel funds at NSHS Bethesda does not preclude a MTF/DTF from sponsoring or co-sponsoring CIP travel from local activity accounts. Each investigator's request (APPENDIX 4), with the endorsement of their CO, should be forwarded via the CID head to CO, NSHS Bethesda (Code OC). Applicants at SFs should route

requests via the CID at the MTF whose IRB has (or had, if the study concluded) official responsibility for original and/or continuing review. CIDs will work with investigators submitting travel requests and their department heads to correct or cancel inappropriate requests (e.g., requests from investigators who were never formally approved study participants, or who joined the study too recently to make meaningful contribution to the manuscript/poster being presented.) CID endorsements should address residual discrepancies if the investigator declines to correct or withdraw an incomplete or improper request. A copy of the presentation abstract, entire meeting brochure (if 20 pages or shorter) and conference sponsor's acceptance letter for the specific presentation must accompany the request. If the meeting brochure exceeds 20 pages, only the full pages that provide the following information need to be provided, 1) conference title, 2) organization that is sponsoring the conference, 3) inclusive conference dates, 4) full street address of conference location, 5) portion of the conference program schedule that specifies the traveler's presentation by date, time, title and name of presenter (commonly not a part of brochure schedules for poster presentations), 6) schedule of all conference fees and charges, and 7) completed registration form. Requests must be submitted to arrive at NSHS Bethesda at least 6 weeks prior to the scheduled travel to assure sufficient processing time. If requests are submitted by telefax, there is no need to provide an additional copy by mail. When travel is completed, the investigator must submit the travel liquidation claim form to the comptroller or Personnel Support Detachment at their local activity, and send a copy of the claim to NSHS Bethesda (Code 11).

(1) Travel Eligibility

(a) The requester must be either a documented principal investigator or federally employed associate investigator (AI) on an approved Navy CI protocol.

(b) The protocol must be in good standing. Travel funds will not be issued if the protocol has been placed on administrative suspension, or has received an adverse study status determination by the IRO.

(c) The presentation must not go beyond the scope of the approved protocol. If any of the following statements pertain, the funding request will not be approved:

1. The abstract is inconsistent with the approved protocol.
- 2 The abstract describes a canceled or terminated protocol, which never acquired sufficient data to enable meaningful analysis.
3. The abstract is incomplete or missing from the application.

(2) Travel Restrictions

(a) Normally, only one investigator will be funded to present the findings of a study at a meeting. However, if the study has multiple major objectives, and each warrants a unique presentation, additional investigators may be funded if each investigator addresses a different major objective of the study.

(b) Travel outside the continental United States will only be approved in very special circumstances.

(c) NSHS Bethesda will fund only meeting/conference registration fees (if any), investigator travel (to and from the meeting) and per diem for travel days plus 3 days at the meeting, which must include the day(s) of the presentation. Payments are regulated by the Joint Federal Travel Regulations. Additional costs, such as course/CME fees, banquet/meal fees, recreation fees, or spouse activity fees will not be funded. Rental car costs will be reimbursed only if the traveler lodges at a Bachelor Officer Quarters (BOQ) removed from the site of the meeting, in a location with inadequate commercial transportation between the BOQ and the meeting site. If the investigator's CO endorses attendance beyond 3 days, or any other non-qualifying activities, the extra expenses must be funded by the investigator's parent command on a split-funding basis.

(d) Travelers who are delinquent providing timely copies of travel liquidation claim forms to NSHS Bethesda Code 11 will not be eligible for additional funding until the delinquency is resolved.

(3) Travel Priorities. The unpredictability of research accomplishment schedules, competition at conference review boards for selection of submissions, and competing priorities for investigator time makes it impossible to accurately predict

the demand for CIP travel funds. To maximize the opportunity for investigators to present research at meetings scheduled late in the fiscal year, no more than two requests from an investigator for funded travel will be considered each fiscal year for travel during October through June. Third and subsequent requests for the period July through September may be approved if funds allow. NSHS Bethesda (Code OC) will periodically issue letters to CIDs, informing them of the status of travel funds, and of any interim policy changes. When it appears that funds will be prematurely depleted, the following categories will be used to prioritize requests:

(a) New Navy investigator making the first presentation of a specific data set and analysis (as an abstract/manuscript/poster) resulting from their first active or recently completed CIP project.

(b) Experienced Navy investigator making the first presentation of a specific data set and analysis (as an abstract/manuscript/poster) resulting from an active or recently completed CIP project.

(c) Navy PI on national cancer treatment group protocols, to attend required headquarters meetings.

(d) Chairs of a CPHS, Institutional Animal Use and Care Committee, or the IRB, or their designees, to attend a research ethics meeting.

(e) New Navy investigator making a subsequent presentation of an already presented specific data set and analysis (as an abstract/manuscript/poster) resulting from their first active or recently completed CIP project.

(f) Experienced Navy investigator making a subsequent presentation of an already presented data set and analysis (as an abstract/manuscript/poster) resulting from an active or recently completed CIP project.

5. NAVY MEDICAL RESEARCH & DEVELOPMENT COOPERATIVE STUDIES. Naval Medical Research and Development projects are funded by Congressionally appropriated "Program 6" (research, development, test and engineering) dollars compared to "Program 8" (operations and maintenance) funds for Defense Health Program health care delivery activities (including CIP support). Both sources of funding can be requested by Navy investigators to support a clinical research protocol with high relevance to

operational (military) medicine. Heads of CIDs are encouraged to inform investigators of the potential availability of R&D funding and technical support at R&D laboratories. The following chain of command and review process is recommended to coordinate R&D processing of requests for joint CIP/R&D funding:

a. Proposal evaluated by review committees at Navy MTF with delegated local approval authority.

b. Approval by CO, MTF with delegated local approval authority.

c. Telephone or telefax inquiry from CID to MED-26 for specific guidance on current procedures and point of contact to obtain R&D review and consideration for cooperative funding.

d. R&D Review.

e. Results of R&D review returned to CID with decision on R&D funding support. The CO of the activity with delegated local approval authority will be responsible for ensuring compliance with all policies and directives pertaining to Navy CIs, regardless of the magnitude of R&D funds that may be provided to support the study.

6 SUPPORT FROM NON-NAVY SOURCES. References (o) through (r) provide guidance. However, directives and policies addressing this topic change frequently. Comptrollers, Judge Advocate General (JAG) corps officers and designated Ethics Counselors should be consulted whenever support is offered from non-Navy sources. Activities should manage and disburse funds received by use of JONs. Depending upon the nature of support, i.e., gift or grant, it may be necessary to return unexpended funds to the provider. In other cases, it may be appropriate to request permission for alternate use. When properly accepted, donated equipment will be added to the local command property inventory; upon completion of the study, the CO will designate the future location and use of donated equipment. Loaned equipment should be appropriately designated on the command's property inventory. Upon completion of the study, return loaned equipment within 30 days.

a. Grants. As defined in reference (p), "a grant is an award of funds, services, or real or personal property from a corporation, foundation, trust, institution, or other entity not organized for profit, and that does not provide any net earnings to shareholders or individuals, for the purpose of stimulating

higher learning or research." Therefore, offers of funds from pharmaceutical companies for product evaluation are not grants and cannot be accepted as such. Additionally, due to the appearance of conflict of interest (i.e., the Federal Government cannot enter an agreement that could result in an apparent product endorsement for a for-profit corporation), such funds should not be accepted even if they could meet the definition of a grant. It may be appropriate to accept funds from a pharmaceutical company if the government provides something in exchange (see ¶7h (2) below).

(1) Applications to federal and non-federal (non-profit organization) grantors of research funds must be endorsed by the local CO.

(2) The grantor must be notified in writing that the grant must be made to the government on behalf of the treatment facility, and is not for personal use of an individual. The original grant application, together with the completed CIP document package will be reviewed by the local JAG and Comptroller and forwarded, with the local CO's endorsement, to the granting agency.

b. Gifts. Per reference (p), a gift is "any donation of funds, services or real or personal property from a non-Federal source for which there is no compensation or promise of compensation on behalf of the donor. A gift may be offered and accepted with or without specified limitations on ownership or use (i.e., may be a condition gift or an unconditional gift)." Policy addressing the acceptance of gifts is very restrictive to minimize any appearance of impropriety. References (p) through (r) should be consulted whenever a gift is offered to a Navy employee or activity. Command ethics and legal advisors can assist with determining the legality and propriety of accepting a gift offer. Comptrollers can assist with the preparation of documents required to process the acceptance, assignment of custody and disposition of a gift. Regardless of circumstances:

(1) Navy Medical Department personnel will not initiate requests for gifts.

(2) Gifts received in support of the CIP must be approved by the chain of command, as described in reference (q). The Chief, Bureau of Medicine and Surgery (BUMED) has received delegated gift acceptance authority from the Chief of Naval Operations for gifts valued at \$10,000 or less.

(3) Study data, intellectual property rights, publication rights, and other considerations commonly expected by and provided to "donors" of investigational agents (e.g., drugs, devices or biologicals) are legally considered "compensation" and disqualify the "donation" from being defined as a gift. This is true even when the agent is not available for sale, and has no market value. Therefore, except in the unusual circumstance where the donor denies current and future interest in any intellectual products of the research, "free" investigational agents usually are not gifts when provided by sponsors or manufacturers for a CI and instead, they need to be addressed in a resource sharing agreement.

C. Henry M. Jackson Foundation for the Advancement of Military Medicine (HMJFAMM)

(1) The HMJFAMM (<http://www.hjf.org>) is a non-profit scientific and educational organization, chartered by Congress in 1983 to support military medical research and education and to promote public-private partnerships. It is a resource for eligible investigators to receive extramural funding (usually provided to the HMJFAMM by for-profit corporations seeking partnerships) in support of clinical research studies. Funds are administered and managed by the HMJFAMM and not by the comptroller of the naval medical facility. For the most part, when funds are made available by the HMJFAMM, civilian personnel issues, procedures for travel and procurement of equipment and supplies are handled by the HMJFAMM. Local MTF policies should be developed that require internal review of investigator requests to the HMJFAMM and that mandate delivery of supplies and equipment to central receiving to help protect both the investigator and the Navy against malicious allegations of waste, fraud or abuse.

(2) The HMJFAMM also administers Special Project Funds and endowment funds to support continuing medical education by means of visiting speakers, travel, supplies, equipment, seminars and meetings. Funds come into the HMJFAMM via multiple sources and are used to support medical conferences, seminars, lectures and training courses.

(3) A memorandum of understanding (MOU), reference (s), between BUMED and HMJFAMM defines how the two parties coordinate efforts to use services available from the Foundation and is currently under review. At this time, local investigators and CIDs are permitted to contact the HMJFAMM directly to obtain information; however, the MOU stipulates that all official

applications to the HMJFAMM for grants or Special Project Funds must be submitted to the Office of Research (Room A1032) at the Uniformed Services University of the Health Sciences and cannot be submitted directly to the HMJFAMM. Eligibility for HMJFAMM research support services requires either a USUHS adjunct academic appointment or a HMJFAMM Guest Scientist appointment. A Guest Scientist appointment requires sufficient professional credentials to qualify for an academic appointment as Assistant Professor at a medical school.

d. Work For Private Parties. "Private Parties" refers to many categories of individuals, companies, and municipalities, which receive services and/or materials from Department of the Navy activities. A general feature of Department of the Navy transactions with private parties is that the private party must provide funds in advance of the services or materials to be received from the Navy. Additionally, private parties are to be assessed full costs for all services provided to them. A pre-condition to providing services or materials to private parties is that the Department of the Navy will not be placed in the position of competing with commercial organizations in the private sector if those services or materials are otherwise available. When a CI is conducted with a for-profit institution, costs must be based on established user charges for fair market value following Comptroller of the Navy directives. The Navy Comptroller's Manual provides detailed guidance. Investigators should consult with their local CID or Navy comptroller concerning current policies, responsibilities, charges and fees for government provided services etc.

7. COLLABORATIONS WITH OTHER INSTITUTIONS. Collaboration is defined as a cooperative effort between two or more investigators, located at two or more facilities, where their participation includes one or more of the following, (1) protocol design, (2) data collection, (3) data analysis, (4) sharing of resources and/or services and/or personnel, or (5) intellectual participation in the preparation of presentations, manuscripts or other documentation of research activity. The sole provision or sale of equipment, resources or services to one party by another is not recognized generally as a collaborative effort.

a. CIP investigators who plan collaborations with colleagues at other institutions must provide evidence of approval by the other activity. IACUC, and/or CPHS/IRB approval should be documented, as applicable. A copy of an appropriately executed Letter of Intent, Memorandum of Understanding (MOU),

Cooperative Research and Development Agreement (CRADA) or other resource sharing agreement, with local comptroller, Judge Advocate General, and CO endorsement, is required.

b. A research protocol that has been thoroughly reviewed and approved for scientific merit through another institution's review system, i.e. IRB or SRC, may be recommended for approval by the local SRC/IRB Chair with respect to scientific design and merit.

c. All protocols must receive full review for human use considerations by the Navy IRB or CPHS specified in the approved Assurance agreement of the Navy MTF or DTF where the PI is employed. The only exception permitted is when that MTF or DTF has an OPRR multiple project assurance that specifically allows it to accept the findings of an IRB at another institution holding an OPRR multiple project assurance and there is an in-force Cooperative Amendment between the two intended collaborating institutions.

d. No DoD activity is allowed to blindly accept or acknowledge the assurance provided by another institution regarding compliance with animal care and use statutes, regulations or standards. The two options for oversight are a DoD IACUC or a local IACUC with verification of compliance via an independent certification agency and/or by a DoD laboratory animal medicine veterinarian. In addition, protocols using cats, dogs, non-human primates or marine mammals must be reviewed and approved by MED-02E.

e. All protocols involving the investigational use of radiation (whether ionizing, ultrasound, or electromagnetic) must be reviewed by the local RSC unless the protocol qualifies for expedited review.

f. All protocols involving retroviral agents must be reviewed by MED-02H. Reference (t) provides policy for review and routing procedures in the case of tri-service retrovirology studies.

g. In the case of collaborations involving Navy medical facilities:

(1) PIs at each site are equally responsible for conducting the research to its completion.

(2) All approved investigators are considered contributors of the data and results, which are the property of the Navy.

(3) The collaboration mandates joint authorship on publications or presentations.

h Appropriate resource sharing agreements must be prepared with the participation and approval of the legal and comptroller's offices and signed by the CO. Activities that routinely participate in collaborative studies are encouraged to develop standard operating procedures that define and streamline the otherwise time consuming internal processes of preparation, routing, approval, and signature of resource sharing agreements for CIs.

(1) The Memorandum of Understanding (MOU) is not legally enforceable in court, regardless of how skillfully it is written. It is probably adequate for documenting most collaborations with other U.S. federal, state and local entities. Other types of agreements are preferable if the collaboration is with other categories of partners. To minimize administrative workload, activities anticipating a prolonged collaboration involving multiple studies may consider trying to negotiate a relatively generic "umbrella" MOU that enables specific studies to be appended as an annex to that MOU.

(2) The Cooperative Research and Development Agreement (CRADA) is the DoD's agreement of choice for collaborations with non-governmental partners (per reference (p)). It defines each partner's contribution to the collaboration and how each will share the research products and profits. The CRADA is an enforceable contract. CRADAs also provide a simple mechanism for accepting funds from the non-government party. In most circumstances, the boilerplate language "Standard CRADA" meets the needs of both parties and is easily prepared. There are no legal or regulatory impediments to the use of CRADAs for CIs. No implementing directive is required from any echelon. CRADAs must be reviewed by the Office of General Counsel at the Office of Naval Research and signed by the Chief of Naval Research unless that authority is delegated locally by the Chief of Naval Research. The Department of Defense (DoD) maintains a directory of numerous sites where staff trained in technology transfer law maintain an Office of Research and Technology Applications (ORTA). ORTA staff can provide both guidance and assistance to local activities. The following World Wide Web sites provide additional information:

(a) CRADA Information: <http://www.onr.navy.mil/sci%5Ftech/industrial/crada.htm>

(b) DoD ORTA Directory: <http://www.dtic.mil/techtransit/business/orta.html>

(c) Technology Transfer Legislation:
<http://www.dtic.mil/techtransit/refroom/laws/>

8. MANUSCRIPTS FOR PUBLICATION OR PRESENTATION. The PI of an approved CI study will ensure that any presentation or publication resulting from that study is prepared, reviewed and submitted following the guidance of reference (u) and identifies the Navy Medical Department CIP as a study sponsor. Include the assigned CIP number in all presentations, publications, or written references to the study. Acknowledgment should be cited as follows:

The Chief, Navy Bureau of Medicine and
Surgery, Washington, D.C., Clinical
Investigation Program sponsored this study
_____.

Data collected during the conduct of CIP studies are property of the Department of the Navy and cannot be released without proper approval authority. To be released, data must be for the benefit of medical science and not for profit. When released for publication, interpretative findings and opinions must be identified as those of the author(s) and not those of the Navy, per reference (u). The following disclaimer must be included verbatim in a prominent place on all manuscripts:

The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U. S. Government.

9. RECOGNITION AND REWARDS. Investigators and research support staff should be officially recognized for excellence in their work or for noteworthy contributions to the research program. Awards should be considered for:

a. Scientific Merit or Relevance. Excellence in research, as evidenced by noteworthy peer group recognition, e.g., publication of a full length article in a prestigious, peer reviewed national or international journal, or jury selected presentation at a prestigious scientific conference.

b. Research Administration. Excellence in the support of the research program.

c. Local CIP Competition. CIDs should sponsor annual competitions where local and SF investigators, in both resident and attending staff categories, may present their CIP research. The competition serves both to recognize investigator efforts and to select competitors for an annual Navy-wide CIP competition. The local competition also can serve to provide recognition and reward efforts in other research categories, such as research-other-than CIP and case. reports.

d. Navy-wide CIP Competition. Annually, the resident and attending staff winners of the CID competitions should present their studies to a panel of unaffiliated judges to determine the best CIP project, Navy-wide. Activities with CIDs are strongly encouraged to host the annual Navy-wide competition on a rotating schedule.

10. CIP STUDY PACKAGE. A research proposal should clearly and comprehensively answer these questions in the written text:

- * What do you intend to do?
- * Why is the work relevant to Navy medicine?
- * What has already been done by yourself and by others?
- * How are you going to accomplish the work?

The CIP study package will consist of two sections:

a. SECTION I. This section contains the research protocol and includes the following items:

(1) Clinical Investigation Title Page and Verification Worksheet (APPENDIX 5), to be submitted with both new proposals and with all requests for modification of previously approved proposals. Paragraphs 1-8 should be completed by the PI prior to submission.

(2) Table of Contents

(3) Research Plan, including:

(a) Abstract - briefly summarize the research proposal.

(b) Specific Aims - concisely and realistically state what the research is intended to accomplish or what hypothesis is to be tested.

(c) Background and Significance - provide a detailed description of the background to the present study, critically evaluating existing knowledge, and specifically identifying the gaps which the study intends to fill. Appropriate references must be cited in context. State concisely the importance of the proposed research by relating the specific aims to the broad long-term objective and to health care relevance. The discussion should include the relevance of the study to Navy Medicine and the general medical community. Two to three pages are normal and recommended for this section.

(d) Preliminary Studies - include a summary of relevant accomplishments (if any) by the proposed investigators to establish their experience and competence to pursue the proposed study. Pertinent preliminary studies may be included in text, but appropriate publications (if applicable) and manuscripts should be submitted as an appendix.

(e) Experimental Design, Materials, Methods and Statistical Analysis subsections - provide a detailed discussion of the experimental design and proposed procedures to accomplish the specific aims of the study. Provide a tentative sequence or timetable for key milestones during the conduct of the investigation. Include how the data will be collected, recorded, stored, protected, analyzed and interpreted, including statistical analysis techniques. Describe any new methodology and its advantage(s) over existing methodologies. Discuss anticipated potential difficulties and limitations of the proposed procedures and potential alternative approaches to achieve the aims. Enumerate any procedures, situations or materials that may be hazardous to personnel or the environment, and the precautions to be exercised (e.g., use of investigational agents, radioactive materials, or biohazardous substances). For studies that incorporate standard of care procedures, clearly specify which aspects of the technical approach are standard of care and which are investigational, i.e., pertain exclusively to participation in the study.

(f) Human Subject Use Justification (if applicable).

1 Identify the sources of research material to be obtained (specimens, records or data). Indicate whether that material will be obtained specifically for research purposes or

whether it has been or will be used for other purposes. Describe the characteristics of the subject population, such as anticipated number, age range, sex, ethnic background, and health status. Identify and justify all criteria for inclusion or exclusion. If pertinent, justify the rationale for using or excluding potentially vulnerable classes of subjects, e.g., pregnant women, active duty members, or children. Additionally, specify the anticipated benefits (if any) to all subjects.

2 Describe plans for recruiting subjects and procedures for obtaining consent, including circumstances when seeking consent, who will seek it, the information to be provided to prospective subjects, and the method of documenting consent. Describe what will be done to minimize coercive recruitment. Provide copies of all recruitment advertisements, scripts, subject information sheets, etc. as an attachment to the study package. *N.B.*, reference (v) prohibits DoD research requiring third party consent unless there is intent to benefit the subjects (personally), and requires the informed consent of the subject (or legally authorized representative) to be obtained in advance.

3 Describe any potential risks (physical, psychological, social, etc.) and assess their likelihood and seriousness. Describe alternative treatments and procedures that might be advantageous to the subjects. Describe procedures to monitor for and protect against (or minimize) any potential risks, including risks to confidentiality, and assess their likely effectiveness. If there is reason to believe that the study will be categorized as "greater than minimal risk", discuss provisions for ensuring unbiased medical or dental monitoring and intervention for the highest risk phase(s) of the study in case of adverse effects to the subjects; identify the physician or dentist, preferably not a member of the investigational team, who has agreed to serve as medical or dental monitor and include their signed memo or letter of intent to serve as monitor, confirming their understanding of their duties.

4. Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to result.

5. In addition to a sample informed consent document, submit a copy of all forms to be used for patient data collection. No data collection instrument should record data

that could easily be linked to a specific subject in the absence of a well protected, coded, subject identifier matrix.

(g) Animal Use Justification (if applicable) - insert the complete DoD mandatory standard protocol format, enclosure (3) to reference (h), which includes justification for the use of animals. The format is very comprehensive, and local activities should carefully consider the cost in study package preparation time and effort before imposing additional document requirements on PIs proposing CIs using animals. CIDs and IACUCs should maintain an up to date library of directives and blank formats pertaining to animal use protocols for the benefit of prospective investigators. MED-02E will periodically provide amplifying guidance pertaining to laboratory animal use for research. NSHS Bethesda will not impose any administrative requirements of its own.

(h) Justification for Investigational Agent, i.e., drug, device and/or biological (if applicable) - reference (x) must be obtained and closely followed. Investigational agents (drugs, devices and/or biologics) to be used in protocols must be adequately justified, stating why present treatment methods are inadequate.

(i) Retrovirology Justification (if applicable) - all CI proposals involving studies with patients identified positive for HIV-1, HIV-2 or HTLV-1 will be screened by the BUMED HIV Program Division (MED-02H) prior to IRO review. Describe in detail the regimen of therapeutic agents to be used (if relevant) and how data will be collected. Outline in detail the parameters to be evaluated, time sequence of proposed clinical trials, long-term follow-up of cases, and security and confidentiality for data, per reference (g).

(j) Bibliography - references must be cited in context, reflect a thorough knowledge of current literature in the area of study, and use a standard format for citation. If a relevant bibliography is sparse or absent for the research topic, documentation of appropriate literature database searches should be provided.

b SECTION II. This section will contain all supporting documents. Seek the advice of CID staff if there is difficulty completing any of the items prior to submission. The following items should be included, if relevant:

- (1) Resource Requirements (APPENDIX 3).
- (2) Department Impact Statement (APPENDIX 6).
- (3) Current curriculum vitae for each investigator, with preparation date noted on the first page.
- (4) Standards of Conduct Acknowledgment Statement (APPENDIX 7).
- (5) Informed Consent Document for Human Use (APPENDIX 8). All subjects must be afforded the opportunity to give free and informed consent to participate in the research. The standards of references (b), (d), and (v) must be incorporated into this document. APPENDIX 8 lists the required and additional elements of informed consent together with sample paragraphs that appropriately address the issues. Reference (g) requires the inclusion of a Privacy Act Statement. The CID office should have a copy of the local informed consent format. APPENDIX 9 is a checklist recommended for use during preparation of consent forms. APPENDIX 10 provides points to consider when preparing research protocols proposing the use of human subjects. Legal review and approval of all consent forms is required.
- (6) Minutes from SRC (if applicable), IRB or SRC and CPHS (to be appended by the local CID).
- (7) Minutes from IACUC (to be appended by the local CID, if applicable).
- (8) Investigational Drug Clinical Information (for investigational drug use, if applicable).
- (9) Manufacturer's Brochure (for investigational device(s), if applicable).
- (10) FDA Forms: FDA-1571, FDA-1572 (for investigational agent use, if applicable).
- (11) MOU, Interservice Support Agreement (ISA) i.e., DD FORM 1144), or CRADA, as required.
- (12) Consultants/Collaborators Letters of Intent (if applicable). If consultant arrangements have been confirmed in writing, attach appropriate confirming letters from each consultant. Describe in detail the support services or

facilities to be provided by consultants, collaborators, consortium and/or contractual agreements and whether those contributions to the study will be provided at the Naval activity or at another site.

(13) Memo or letter of intent from medical/dental monitor (for studies anticipated to be categorized as greater than minimal risk)

11. ROUTING THE CIP STUDY PACKAGE

a. By the PI. After the PI has completed the CIP study package, it must be reviewed and endorsed by the Research Coordinator and/or PI's department chair. This review and endorsement provides an opportunity for mentoring, quality improvement and coordination with other local CIs. The endorsement is not intended merely to formalize an immediate supervisors' acknowledgment that a proposal is being submitted. Endorsement constitutes a professional scientific and ethical opinion on the part of the Research Coordinator and/or department chair commensurate with a published opinion in the open literature. Upon favorable endorsement(s), the study package is submitted next to the head, CID, if the PI is employed at a MTF or DTF with a CID. At SFs, the study package requires local review, followed by favorable endorsement by the SF's CO before routing to the supporting MTF's CID. Retrovirology studies may be submitted to the CID via BUMED (MED-02H) or copies may be submitted to both addressees concurrently to speed processing. The activity may request MED-02H to forward acceptable packages to the designated CID, but return unacceptable proposals to the originating site.

b. By the CID. The head, CID is responsible for routing the study package to appropriate review committees, advisors (e.g., fiscal or JAG officer) and to the CO after IRO review. The head, CID will assign a study number according to the system described in APPENDIX 11. Document tracking and internal routing controls should be described in a CID Standard Operating Procedure.

(1) Animal Use Protocols. A copy of all animal use protocols proposing the use of cats, dogs, marine mammals or non-human primates must be forwarded to MED-02E upon completed, favorable action by the IACUC. Favorable endorsement by MED-02E must be obtained before a study package is routed to the CO for final approval. One complete copy of all approved animal use

CIP protocols will be forwarded to NSHS Code OC for information and reference.

(2) R&D Collaborative Efforts. Inquiries should be addressed to the BUMED Director, Research and Development (MED-26).

(3) Henry M. Jackson Foundation for the Advancement of Military Medicine. For proposals anticipating critical HMJFAMM support, it may be prudent for CIDs to verify PI eligibility for HMJFAMM services with the HMJFAMM, prior to submitting those proposals to their IRO, in order to avoid unnecessary IRO workload. After CO's approval, the cover letter and a copy of the research protocol package should be submitted to Office of Research (Room A1032) at USUHS (not sent directly to the HMJFAMM). The protocol will be reviewed by USUHS for qualification under either the USUHS adjunct faculty or the guest scientist rules and forwarded to HMJFAMM if qualified.

12 PERIODIC AND SPECIAL REVIEWS. Reference (d) requires IROs to 'periodically re-evaluate non-exempt human subjects research at intervals appropriate to the degree of risk, but not less than once per year. These "continuing reviews" should, as a minimum, address the criteria described in the FDA information sheet *Continuing Review After Study Approval* dated, September 1998 and in the section "Continuing Review" in the *Protecting Human Subjects Institutional Review Board Guidebook*, published by OPRR in 1993. Note that one criterion for continued IRO approval is "research results obtained thus far." CIDs should use APPENDIX 12 (Clinical Investigation Periodic Review) as part of the routine administrative package supporting their CPHS/IRB's continuing review process. CIDs may use a locally prepared form in place of APPENDIX 12 if that form does not delete any item from the appendix. The continuing review form will be retained in CID files after action is completed by the CPHS/IRB and accepted by the CO. Both principal and associate investigators have the responsibility for filing reports and cooperating with their IRO and CID. Investigators must notify their CID head about all circumstances regarding an inability to provide necessary information in a timely manner. Special reviews can be required by the CPHS/IRB at any time prior to the next scheduled continuing review, if requested by a majority of a quorum of voting members.

a. CPHS/IRB Study Status Determination. The following paragraphs define the actions that CPHS/IRBs can take after

reviewing a study. The study status must be noted in the CPHS/IRB meeting minutes.

(1) **Approved for continuation** until the next scheduled continuing review. The study is considered in good standing and funds targeted to enable the project may be obligated and expended, including reprint costs for published manuscripts. Research reports may be prepared for possible presentation or publication. Investigators are eligible to apply for travel funds from NSHS Bethesda for presentation of findings. However, if no project activity is reported for the preceding 12 months, the reviewing authority should consider terminating the study.

(2) When study objectives have been met and no subject follow-up is required, the study is considered **completed**. The investigators are eligible to apply for reprint costs from the CID as well as for travel funds from NSHS Bethesda for presentation of findings. A **completion report** must be submitted by the PI to the CID within 30 days of study completion. The report should provide a summary (including an abstract) of project objectives, methods, results, and conclusions, and a complete bibliography of all publications and presentations resulting from the study, in a format suitable for publication. The report should also discuss the likelihood and venue of future publications and presentations of study data. All income and expenditures, regardless of source, for the entire study, must be included. CIDs will forward a copy of the completion report to NSHS Bethesda (Code OC) within 30 days of receipt.

(3) A study may be **suspended** by the CPHS/IRB, or unilaterally by the chair during evaluation of adverse events, infractions involving noncompliance with CPHS/IRB requests for information, or for infractions involving human use and/or animal use guidelines. If unilaterally suspended by the chair, the issue will be an agenda item at the next regularly scheduled CPHS/IRB meeting. If suspended, the study is:

(a) No longer eligible for funding except for costs associated with medically indicated follow-up of currently enrolled subject/patients.

(b) No longer open to subject enrollment.

(c) Not active for already enrolled subjects, unless subject/patient medical welfare would be threatened by protocol suspension.

(d) Not eligible for CIP travel funding until the information requested has been provided and/or the CPHS/IRB is satisfied that the study's investigative team is sufficiently educated to minimize the risk of recurrent infraction. A suspended study may be reinstated to an approved status or modified to a completed status. Once suspended, failure to resolve the cause for suspension after 30 additional days justifies but does not require termination.

(4) A study may be **terminated** due to serious or recurring minor adverse events, lack of progress, major noncompliance with human use, animal use, or reporting requirements (or habitual minor noncompliance violations), or a demonstrated lack of interest by the investigators. However, if enrolled subjects require future follow-up in accordance with the protocol, the study may not be terminated. In that case, the issue(s) warranting termination should be presented by the chair, CPHS/IRB to the PI's CO via the chain of command for alternate means of resolution. Once a study is terminated, no funds may be used to support any further work on that study except as may be medically indicated for enrolled subjects, and investigators are no longer eligible for CIP funded travel related to that study. If termination is due to major noncompliance, CPHS/IRBs are advised to consider an early continuing review of all other studies involving the noncompliant investigator(s). If a protocol has been terminated, the PI may request reinstatement within 30 days, if all information requested by the CPHS/IRB is provided, together with a newly signed assurance by all investigators that the protocol will be expeditiously accomplished in accordance with all relevant guidance and directives pertaining to clinical investigations. The PI's **termination report** (or a request for reinstatement) is due at CID within 30 days of written notification to the PI of study termination. The report shall contain an explanation for termination and a summary of work accomplished to the date of termination, including citations for all associated publications and presentations. All income and expenditures for the entire study, regardless of source, must be included. CIDs will forward a copy of the termination report to NSHS Bethesda (Code OC) within 30 days of receipt.

b. CID Study Status Determination. CID heads may impose **administrative suspension** on a study for as long as 30 days in cases of investigator noncompliance with appropriate CID requests for information, reports, or meetings. After 30 days, unresolved noncompliance will be referred to the chair, CPHS/IRB as an agenda item for the next regularly scheduled meeting. The

suspension will remain in force pending CPHS/IRB disposition of the issues. Administrative suspension imposes the same restrictions as CPHS/IRB directed suspension described in ¶8a(3).

13. RECORD KEEPING. Permanent records of all CIP related documents are potentially releasable under the Freedom of Information Act and/or subject to audit by either the OPRR or the FDA and normally will be maintained at local CID offices. If preferred, files of CIP studies that have been completed and/or terminated for at least three years can be moved off-site provided that they have been copied on to uneditable media, e.g., microfiche or write-once CD-ROM, and reliable hardware is available in CID to read and print out data from that media. Security for the storage media and access to reader software must be sufficient to protect the integrity and confidentiality of the data. Records include (but are not limited to):

- a. Copies of all study packages (SECTIONS I & II), and approved modifications, amendments, updated informed consent forms, patient information packages, subject recruitment media, opinions from MED-02E and MED-02H (if applicable), official communications with CID or investigators pertaining to the study, and completion/termination reports.
- b. Initial and all updated c.v.s for investigators.
- c. Identification data on patients enrolled in each study.
- d. Copies of Continuing Review reports from IRO staff and adverse event reports (if any).
- e. Approved (signed) minutes of IRO and other advisory committee meetings.
- f. For studies using investigational agents, forms and reports required by reference (x) and by multiple parts and sections of Title 21, Code of Federal Regulations as well as any communications with the FDA.
- g. Enabling collaborative support agreements.
- h. Fiscal records that document the JON(s) assigned to each study, funds allocated, and all obligations and expenditures for those JON(s).

i. Any and all CIP/CID related inspection and audit reports, performed internally (as part of a department or command quality assessment or quality assurance program) and externally (e.g., OPRR, FDA, Joint Commission on Accreditation of Healthcare Organizations, NSHS Bethesda, etc.).

j Dated education and training materials for investigators and for IRO staff, with attendance sheets or distribution lists.

14. SECURITY OF PRIVACY ACT INFORMATION. Confidentiality of records identifying research subjects will be maintained. The following rules apply:

a. No easily deciphered subject identifiers, including but not limited to names, initials or SSNs, will be placed on data sheets or in subsequent publications or presentations. Written matrices that correlate subject identifiers to study code numbers must be kept securely locked; electronic matrices must use software that enables files to be password protected. Passwords should be non-intuitive. Exercise caution to ensure that all backup copies of these files are password protected.

b All databases will be maintained on electronic media using software that enables data files to be password protected. Passwords should be non-intuitive and known only to the investigators. Exercise caution to ensure that all backup copies of these files are password protected.

c. All CIP records are Federal property. Records containing Privacy Act information will be maintained in locked containers in locked Federal offices or official Federal archive sites in perpetuity.

15. REQUIRED DOCUMENTATION TO NSHS BETHESDA. Timely delivery of postal mail to NSHS Bethesda (Code OC) has historically been unreliable. Sites should inform Code OC of their preferred method to track mail. Logical alternatives include either providing Code OC with an e-mail or telefax notification of items mailed within one day of mailing, or establishing a "tickler" system to determine the status of previously mailed items if not acknowledged by Code OC in an appropriate interval. The following documents must be provided to NSHS Bethesda (Code OC), either to comply with Federal Code and other higher authority directives, or to justify and secure funding for Navy CIP projects:

a. Assurance of Compliance with the Federal Policy for the Protection of Human Subjects. Each institution engaged in human subjects research shall provide written assurance that it will comply with the requirements of reference (d). The detailed implementation of the Assurance process for DoD is reference (w), which should be consulted for details and may be obtained upon request from NSHS Bethesda (Code OC). The policy pertains to all DoD facilities located both within CONUS and OCONUS. Unless the institution provides evidence of a relevant, approved Multiple Project Assurance from OPRR, approval of a written DoD Assurance and the assignment of an accompanying Assurance number by NSHS Bethesda (Code OC) is required before any non-exempt, CI involving humans subjects may be conducted in a Navy MTF or DTF. In all cases, determination of "exempt" must be made officially by the authorized individual at a supporting MTF.

b. IRO Minutes. CIDs must ensure that one copy of every set of CO signed CPHS or IRB minutes is forwarded to NSHS Bethesda (Code OC) within 30 days of CO's signature. To conserve paper and minimize mailing costs, a full copy of relevant minutes should not be attached to each study subsumed by those minutes when those study packages are forwarded to NSHS Bethesda. However, all new and changed study packages provided to NSHS Bethesda (Code OC) must specify the meeting date of the CPHS/IRB quorum that recommended the administrative disposition for that study. For new studies, that date should be entered in ¶11a on the Clinical Investigation Title Page and Verification Worksheet (APPENDIX 5). For changed studies, that date should be entered on the communication to the PI providing notification of approval of the changes.

c. New Studies. A copy of the entire study package should be provided to NSHS Bethesda within 30 days of the CID's letter to the PI that provides notification of unconditional approval. A copy of that written communication to the PI (copy to NSHS Bethesda) is acceptable as the forwarding cover letter to NSHS Bethesda. For studies originating at SFs, a copy of the local CO's initial certifying letter and any certifying letter(s) for changes submitted in response to IRO requested/required modifications, should be included in the study package. To conserve paper and minimize mailing charges, CIDs may request that NSHS Bethesda establish a c.v. file for their investigators. In that case, if the same version of any investigator's c.v. has previously been provided to NSHS Bethesda, a spacer sheet containing the investigator's name, and the month and year of that c.v. version should be substituted for the c.v. print out.

d. Changes in Research Protocol. Any modification to an approved study requires review by the IRO and if appropriate, by cognizant local advisory boards. If the study involves the use of cats, dogs, marine mammals or non-human primates, MED-02E must review the proposed change(s) in addition to the IACUC. A copy of CO signed IRO minutes documenting approval of study changes (and local CO certification of the changed items, in the case of SFs) should be submitted to NSHS Bethesda (Code OC) accompanied by-a copy of the changed documents accepted by the IRO (in addition to a copy of the documents described below, if relevant). A copy of the written communication to the PI (copy to NSHS Bethesda) that formally notifies the PI of the CO's decision is acceptable as the forwarding cover letter to NSHS Bethesda. Guidance immediately above, in sections a. through c addressing forwarding deadlines, IRO minutes and c.v.s pertains as well to modification packages. Approved changes and their associated review and approval documentation must be added, never substituted, for a previously approved version of those documents in all CIP files (e.g., CID, IRO, PI, etc.).

(1) Deletion of Investigator. The deletion of an investigator should be documented in writing by PI submission of APPENDIX 7 to the head, CID. When an AI is deleted, the personnel data section for that AI should be completed and signed by the AI to signify acknowledgment of withdrawal from the study.

(2) Addition of New Investigator. The addition of an investigator should be documented in writing by PI submission of APPENDIX 7 to the head, CID. Only the signature and data pertaining to the added investigator (and accompanying c.v.) need be provided in the personnel data section of APPENDIX 7. However, if the new addition is to be the new PI, personnel data should be provided for both the outgoing and the new PI. The new PI should complete and sign the bottom of the form and the outgoing PI should sign the relevant personnel data section to acknowledge the change in status. If the study uses human subjects, and the PI has changed, submit the revised Informed Consent Document(s) as part of the package. Although changes in AIs may qualify as minor changes that are eligible for IRB approval by expedited procedures, changes in PI should always be considered a substantive change, and will require consideration by a quorum of the IRB (unless the study was previously approved by expedited procedures).

(3) Study Amendment. CIDs may require investigators to submit only the changed and/or appended pages, or they may require PI re-submission of the entire section or even the entire study package incorporating the required change(s). Revised (changed) or added pages shall include a centered header on each page in the format, "Revised __, __" for pen and ink completion by CID with the month and year of final CO's approval. To obviate the need to renumber unchanged pages and regenerate the table of contents, added pages shall be numbered by including letters of the alphabet to the last page number in the originally approved version of the protocol. For example, if seven pages are required to replace pages 6-8, they should be numbered 6, 7, 8, 8a, 8b, 8c and 8d. Similarly, if the revision reduces the page count, the blank pages should be retained, contain the revised date header and be marked, "This Page Intentionally Left Blank." However, in the case of revised informed consent documents, use one of two alternate methods of marking these documents, even when only selected pages are revised. Either update the header on every page so that the version date is consistent or, when applying an IRB approval stamp with the updated approval date, stamp each and every page of the revised document. In other words, each page of a revised informed consent document should contain the same, updated date. The package for NSHS Bethesda should contain a copy of the approved revised and/or added pages and the memo to the PI from CID that forwards the approved amendment and specifies the date of the CO approved CPHS/IRB minutes that recommend approval of the amendment.

e. Reports Pertaining to Research Using Investigational Agents. Reference (x) specifies Navy policy for research with human subjects using investigational drugs, biologicals and devices. These studies have special reporting requirements, which are more extensive than for other categories of CIs. Reference (x) should be consulted for detailed guidance. A completely prepared, revised Food and Drug Administration (FDA) form FDA-1572 must be submitted to the FDA whenever investigators are added or deleted. For Navy sponsored studies, a revised FDA-1571 will need to be prepared and submitted when there are changes affecting Blocks 14 - 16.

f. Annual Data Summary Report for Director's Briefing to the Office of Assistant Secretary of Defense for Health Affairs. Each year, USUHS and the three Armed Services CIP program officers are required to brief the status of their program to senior staff in the office of the ASD(HA). The briefing is usually conducted in the Spring, using a common format specified

by ASD(HA) and focuses on data that describes CIP activities during the preceding fiscal year. The service CIP Directors have agreed to use a common spreadsheet template (which has been distributed to CIDs) to facilitate data collection and transmission. Assuming no late changes to the data set or briefing schedule, CIDs have approximately 4 months to prepare their submission, which should include data from the satellite facilities they support. Unless informed otherwise, CIDs should assume that each year's data elements will be identical to the preceding year's set. NSHS Bethesda (Code OC) will immediately forward format or content changes from ASD(HA) to the CIDs to maximize the CIDs' opportunity to provide complete and accurate data.

g. Completion and Termination reports. See ¶12.a.(2) and ¶12.a.(4).

h. Adverse Study Status Determinations. On occasion, studies may be suspended (see ¶12a(3) and ¶12b) or terminated (see ¶12a(4)) due to investigator non-compliance. Copies of suspension or termination notifications (and subsequent reinstatement notifications, if any) to investigators should be provided to NSHS Bethesda, Code OC by telefax on the day that they are provided to the affected investigator(s).

i. Adverse Event Reports. The Research Coordinator (in the case of SFs), the CID (or supporting CID in the case of SFs), and NSHS Bethesda (Code OC) must be notified within 1 normal duty day of any untoward event occurring during the conduct of a CI that justifies the preparation of an "incident report" (or similar report) to a local internal oversight office, such as the Director of Nursing, Director of Clinical Services, or Risk Management Committee. A telefax of the local reporting form will be sufficient if the form is legible and the CIP study number, study title, and name of the PI is included. Both the CID and NSHS Bethesda (Code OC) must be kept fully informed of the clinical outcome of the adverse event, if resolution was not apparent when the initial report was prepared. In the case of studies using FDA investigational agents, additional reporting requirements may exist, per reference (x).

REFERENCES

- (a) **DoD DIRECTIVE 3216.2** Protection of Human Subjects in DoD Supported Research, of 7 Jan 83
- (b) **SECNAVINST 3900 39B** Protection of Human Subjects
- (c) **BUMEDINST 6000.12A** Clinical Investigation Program
- (d) **TITLE 32 CFR Part 219** Public Welfare, Protection of Human Subjects
- (e) **TITLE 21 CFR Part 50** Food and Drugs, Protection of Human Subjects
- (f) **TITLE 21 CFR Part 56** Food and Drugs, Institutional Review Boards
- (g) **SECNAVINST 5211.5D** Privacy Act Program
- (h) **OASD(HA) memo**, Department of Defense (DoD) Policy for Compliance with Federal Regulations and DoD Directives for the Care and Use of Laboratory Animals in DoD-Sponsored Programs, of 10 Apr 95
- (i) **DoD Directive 3216.1**, The Use of Animals in DoD Programs, of 17 Apr 95
- (j) **TITLE 9 CFR Chapter 1, Subchapter A** Animal Welfare
- (k) **SECNAVINST 3900.38B**
- (l) **BUMEDINST 3900.8** Written Animal Use Proposals
- (m) **NAVMED P5055** Radiation Health Protection Manual
- (n) **BUMEDINST 6470.10A** Initial Management of Irradiated or Radioactively Contaminated Personnel
- (o) **DOD DIRECTIVE 5500.7**, Standards of Conduct
- (p) **DoD DIRECTIVE 6000.8**, Funding and Administration of Clinical Investigation Programs, of 3 Nov 99
- (q) **BUMEDINST 4001.4A** Acceptance of Gifts
- (r) **SECNAVINST 4001.2G** Acceptance of Gifts
- (s) **MOU between NAVMEDCOM and HMJFAMM of 23 Sep 88**
- (t) **MOU Among the Surgeons General of the Army, Navy and Air Force of Sep 1994**
- (u) **BUMEDINST 5721.3** Approval Process for Publication of Professional Manuscripts and Articles
- (v) **TITLE 10 USC Section 980**
- (w) **OASD(HA) memo**, Department of Defense (DoD) Guidance for Assurance of Compliance with the Federal Policy for the Protection of Human Subjects, of 10 Jun 93
- (x) **BUMEDINST 6710.69** Use of Investigational Agents in Humans

APPENDICES

Note: Appendices printed locally at CIDs and SFs may substitute a local header for the header that provides the NSHS instruction number/date. The "APPENDIX #(Page#)" portion of the title and the NSHS instruction page number footer may be deleted.

1. **ACRONYMS AND DEFINITIONS**
2. **CLINICAL INVESTIGATION DEPARTMENT AREA RESPONSIBILITIES**
3. **CLINICAL INVESTIGATION RESOURCE REQUIREMENTS**
4. **REQUEST TO CIP FOR TRAVEL FUNDS**
5. **CLINICAL INVESTIGATION TITLE PAGE AND VERIFICATION WORKSHEET**
6. **DEPARTMENT IMPACT STATEMENT**
7. **INVESTIGATOR'S ACKNOWLEDGMENT OF STANDARDS OF CONDUCT
AND/OR CHANGE OF INVESTIGATOR REPORT**
8. **SAMPLE INFORMED CONSENT DOCUMENT FOR HUMAN USE RESEARCH
PROPOSALS**
9. **CONSENT FORM CHECK LIST**
10. **POINTS TO CONSIDER FOR PROTOCOLS USING HUMAN SUBJECTS**
11. **ASSIGNING CIP NUMBERS TO RESEARCH PROPOSALS**
12. **CLINICAL INVESTIGATION PERIODIC REVIEW**

APPENDIX 1 (Page 1)
ACRONYMS AND DEFINITIONS

AI	Associate Investigator.
ASD (HA)	Assistant Secretary of Defense (Health Affairs).
BUMED	Navy Bureau of Medicine and Surgery.
CERTIFICATION	A written communication by an authorized official at an institution with a valid Assurance (normally the CO), verifying that a specific proposal for research has been reviewed and approved by the designated IRB/CPHS and is favorably endorsed for implementation. At supporting MTFs, this communication is accomplished by the Commander's approval of IRO minutes. At SFs, certifications are prepared upon notification of approval by the IRB/CPHS of record.
CI	Clinical Investigation/Research. A research program, project, task, test, experiment, record review, evaluation, or similar undertaking that uses data collected from DoD health care beneficiaries, laboratory animals, or in vitro to study the maintenance of health or the prevention, alleviation or cure of disease, and whose primary purpose is designed with the intent to develop or contribute to generalized knowledge. The terms "research", "clinical research", "clinical study" and "clinical investigation" are deemed synonymous.
CID	Clinical Investigation Department. Each CID will act as local or regional program manager for clinical investigations within its area of responsibility. The Commander/Commanding Officer of each MTF and DTF with a CID has responsibility for the implementation of his/her local program.
CIP	Clinical Investigation Program. The system of directives, offices, and personnel that enable clinical research within the Department of the Navy.
CO	Commanding Officer.

APPENDIX 1 (Page 2)
ACRONYMS AND DEFINITIONS

CPHS	Committee for the Protection of Human Subjects.
CRADA	Cooperative Research and Development Agreement.
DoD	Department of Defense.
DTF	Military Dental Treatment Facility.
FDA	Federal Food and Drug Administration.
NSHS	Naval School of Health Sciences, Bethesda.
HMJFAMM	Henry M. Jackson Foundation for the Advancement of Military Medicine.
HIV	Human Immunodeficiency Virus.
IACUC	Institutional Animal Care and Use Committee.
IDCI	Investigational Drug Clinical Information Brochure.
IRB	Institutional Review Board.
IRO	Institutional Review Organization. IROs can be configured as either an IRB or separate SRC and CPHS committees.
ISA	Interservice Support Agreement.
JAG	Judge Advocate General Corps.
JON	Job Order Number.
MOU	Memorandum of Understanding.
MTF	Military Medical Treatment Facility.
PI	Principal Investigator.
RSC	Radiation Safety Committee.
SECNAV	Secretary of the Navy.

APPENDIX 1 (Page3)
ACRONYMS AND DEFINITIONS

SF	Satellite Facility. Any Navy activity where a CI can be certified, which does not have a CID. cos of SFs are responsible for program implementation at their facility.
SRC	Scientific Review Committee.
SSN	Social Security Number. .
USUHS	Uniformed Services University of the Health Sciences.

APPENDIX 2
CLINICAL INVESTIGATION DEPARTMENT
AREA RESPONSIBILITIES

National Naval Medical Center, Bethesda, MD: All Navy MTFs, DTFs and branch clinics in - Connecticut, Delaware, Florida, Illinois, Indiana, Maine, Maryland, Massachusetts, Michigan, Naval District Washington D.C., New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, Vermont, Wisconsin, and in Bahrain, England, Germany, Greece, Italy, Scotland and Spain.

Naval Medical Center, Portsmouth, VA: All Navy MTFs, DTFs and branch clinics in - Alabama, Arkansas, Georgia, Iowa, Kentucky, Louisiana, Minnesota, Mississippi, Missouri, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia (excluding Naval District Washington D.C.), West Virginia, and in Cuba, Puerto Rico and Iceland.

Naval Medical Center, San Diego, CA: All Navy MTFs, DTFs and branch clinics in - Alaska, Arizona, California, Colorado, Hawaii, Idaho, Kansas, Montana, Nebraska, Nevada, New Mexico, North Dakota, Oregon, South Dakota, Utah, Washington, and Wyoming, and in Diego Garcia, Guam, Japan and Korea.

APPENDIX 3 (Page 1)
CLINICAL INVESTIGATION RESOURCE REQUIREMENTS

CIP#: _____

1. PI: _____

2. TITLE: _____

3. FACILITIES AND RESOURCES REQUIRED:

a. Human Subjects:

# Experimental:	_____	Source:	_____
# Control:	_____	Source:	_____
# Minors:	_____	Ages:	_____
TOTAL#:	_____		

b Animal Model:

<u>Species</u>	<u>Strain</u>	<u>Sex</u>	<u>Wt/Age</u>	<u>Total#</u>	<u>Use Rate</u>

c. Investigational Agents:

Description: _____
Source: _____
Sponsor: _____
IND/IDE#: _____
IDCI: _____

d. National Oncology Group Protocol:

Which group? _____
Which protocol? _____

e. Is A MOU Required? (Check with CID) ☐ Yes ☐ No

Name of other institution(s): _____

APPENDIX 3 (Page 2)
CLINICAL INVESTIGATION RESOURCE REQUIREMENTS

f. Is An ISA Required? (Check with CID) ☐ Yes ☐ No
Name of other institution(s): _____

g. Is a CRADA Required? (Check with CID) ☐ Yes ☐ No
Name of other institution(s): _____

4. SOURCE OF SUPPORT (check boxes that pertain):

a. ☐ CIP (Travel) \$ _____

b. ☐ GRANT \$ _____

c. ☐ GIFT \$ _____

d. ☐ HMJFAMM \$ _____
☐ Adjunct Faculty, USUHS (Department: _____)
☐ Guest Scientist Status ☐ MOU-HIV Study

e. ☐ OTHER \$ _____ Source: _____

f. ☐ Only Services and/or Supplies (Source: _____)

5. TOTAL MAN YEARS OF SUPPORT: Military: _____ Civilian: _____

6. SALARIED PERSONNEL:

NAME	POSITION	TOTAL HOURS	SALARY

APPENDIX 3 (Page 3)
CLINICAL INVESTIGATION RESOURCE REQUIREMENTS

7. BUDGET Target Completion Date: _____
FIRST AND SUBSEQUENT 3 YEARS(per fiscal year):

CATEGORY	YEAR 1	YEAR 2	YEAR 3	YEAR 4
(EXPENSE ELEMENT)				
Personnel(U)				
Rental(M)				
Preventive Maintenance For Equipment(P)				
Purchased Services & Contracts (Q)				
Supplies (T)				
Non-Investment Equipment (W)				
Investment Equipment(W)				
Printing & Reproduction (Y)				
Other Expenses (Specify)				
TOTAL DIRECT COSTS	\$	\$	\$	\$
TRAVEL	\$	\$	\$	\$

(Signature, Principal Investigator) (Date)

EXPENSE ELEMENT DEFINITIONS:

(U) Personnel. Salary and benefits only for those civilians directly assigned to work on the study, for the percentage of their time assigned to the study.

(M) Rentals. Contract costs for equipment rental(s) should be included here, not in expense element "Q."

(P) Preventive Maintenance For Equipment. Include salary costs (if any) for personnel performing the maintenance, items purchased to accomplish maintenance, and the cost of preventive maintenance contracts, if any (not in expense element "Q").

APPENDIX 3 (Page 4)
CLINICAL INVESTIGATION RESOURCE REQUIREMENTS

(Q) Contracted Services. Letters of intent are required from each consultant. Costs may include the expense of sending specimens to another laboratory if your facility cannot conduct the required testing. Contractual arrangements warrant a categorical breakdown of costs and an explanation of the method used to compute payment. Documentation of fiscal, legal and CO approval, together with a copy of the agreement, must accompany this submission.

(T) Supplies. Expendable items used to perform the research.

(W) Non-Investment Equipment. Equipment costing <\$100,000.
Investment Equipment. Equipment costing >\$100,000.

(Y) Printing & Reproduction Costs. Presentation media (slides, posters, handouts, etc.) and published manuscript reprints.

Total Direct Costs. Total all justified costs, on a fiscal year (1 October - 30 September) basis.

Travel. Travel funds to support presentations of approved CIP projects are usually available at NSHS Bethesda, and are centrally managed. If NSHS cannot fund a presentation, the local command may elect to provide funds. Indicate the approximate cost of travel to be requested for each fiscal year.

TO BE COMPLETED BY CID:

Project Approval by IRB, Date: _____

CO Signed IRB Minutes, Date: _____

Letter from CID to PI (Unconditional Approval to Start),
Date: _____

Estimated Project Stop Date: _____

JON(s)
Assigned: _____

APPENDIX 4 (Page 1)
REQUEST TO CIP FOR TRAVEL FUNDS

6500
Ser/
(Date)

From: Commander, Investigator's Command
To: Commanding Officer, Naval School of Health Sciences
(Code OC), Bethesda, Maryland 20889-5611

Subj: REQUEST FOR TRAVEL FUNDS FROM THE CLINICAL INVESTIGATION
PROGRAM (CIP)

Encl: (1) Presentation Abstract
(2) Meeting Brochure (Complete)
(3) Acceptance Letter

1. CIP travel funds are requested for:

- a. Name (specify whether PI or AI), Rank, SSN, Location:
- b. CIP Number:
- c. CIP Title:
- d. Organization Sponsoring The Meeting, Proposed Dates And
Location:
- e. Presentation Title:

2 A copy of the abstract is forwarded as enclosure (1).
Enclosure (2) provides information about the meeting. The
letter of acceptance of abstract is provided as enclosure (3).

3. The estimated costs include:

Travel	\$
Per Diem	\$
Fees	\$
Misc.	\$
TOTAL	\$

4. If you have questions concerning this request, please
contact _____ at telephone number _____. The telefax
number is _____. The e-mail address is _____.

5. This ☐ is / ☐ is not the first ever Navy CIP presentation I
will make. This is the ☐ 1st ☐ 2nd ☐ 3rd Cl 4th request for
CIP travel funds that I have submitted during this fiscal year.

SIGNATURE

APPENDIX 4 (Page 2)
REQUEST TO CIP FOR TRAVEL FUNDS

CID's Recommendation: ☐ APPROVE ☐ DISAPPROVE

If disapproval is recommended, state why: _____

(Signature, Head, CID)

(Date)

APPENDIX 5 (Page 1)
CLINICAL INVESTIGATION TITLE
PAGE AND VERIFICATION WORKSHEET

CIP#: _____

Date Submitted: _____ Projected Study Duration: _____

1. PI: _____

2. Title: _____

3. Performance Site (Institution/Department): _____

Other Institution(s) (Collaboration): _____

Has this protocol been submitted for approval to CPHS/IRBs
at other institutions concerned? ☐ Yes ☐ No

If yes, where? _____

Their disposition (attach copy)? _____

4. Personnel Engaged On Project:

NAME/GRADE/SSN	STATUS*	LOCATION
----------------	---------	----------

PI: _____

AI: _____

AI: _____

AI: _____

AI: _____

AI: _____

*STATUS: Trainee (T), Staff (S), Civilian (C)

5. Support Requested From: ☐ CIP ☐ HMJFAMM ☐ GRANT ☐ GIFT
☐ OTHER (Specify _____)

6.** Support Requires: ☐ MOU ☐ ISA ☐ CRADA ☐ CONTRACT

**Ask CID for assistance

7. Principal Investigator: _____

(Signature) (Day/Mo/Yr)

8. Action by Department Chair: ☐ APPROVE ☐ DISAPPROVE

(Department Chair's Signature) (Day/Mo/Yr)

9. Accepted for CID Processing: _____

(Signature, Head, CID)(Day/Mo/Yr)

APPENDIX 5 (Page 2)
CLINICAL INVESTIGATION TITLE
PAGE AND VERIFICATION WORKSHEET

10.

RESEARCH INVOLVES OR REQUIRES

APPROVAL DATE
(Day/Mo/Yr):

PENDING/APPROVED

INITIALS

	YES	NO			
Scientific Review	<input type="checkbox"/>	<input type="checkbox"/>	SRC/IRB	_____/____	_____
Humans	<input type="checkbox"/>	<input type="checkbox"/>	CPHS/IRB	_____/____	_____
Investigational Agents	<input type="checkbox"/>	<input type="checkbox"/>	IDE/IND	_____/____	_____
Retrovirus	<input type="checkbox"/>	<input type="checkbox"/>	MED-02H	_____/____	_____
Radiation	<input type="checkbox"/>	<input type="checkbox"/>	RSC	_____/____	_____
Animals	<input type="checkbox"/>	<input type="checkbox"/>	IACUC	_____/____	_____
Nonhuman Primates, Cats, Dogs, Marine Mammals	<input type="checkbox"/>	<input type="checkbox"/>	IACUC	_____/____	_____
	<input type="checkbox"/>	<input type="checkbox"/>	MED-02E	_____/____	_____
Collaboration	<input type="checkbox"/>	<input type="checkbox"/>	Agency/ Institute	_____/____	_____
CRADA/MOU/ISA/CONTRACT			Effective Date:	_____	Exp. Date: _____
Satellite Facility	<input type="checkbox"/>	<input type="checkbox"/>	Local	_____/____	_____
			co		
11.	Action by Naval Medical Center _____:				
	(location)				
a.	Approval recommended, per CPHS/IRB meeting of: _____				
	(Day/Mo/Yr)				
b.	CO signed CPHS/IRB minutes: _____				
	(Day/Mo/Yr)				
c.	Unconditional start letter from CID to PI: _____				
	(Day/Mo/Yr)				
d.	Approval Authority: _____				
	(Signature, by direction approval authority) (Day/Mo/Yr)				
12.	Action by NSHS OC: <input type="checkbox"/> Approved <input type="checkbox"/> Disapproved				
	Signed: _____ (Day/Mo/Yr)				

APPENDIX 6
DEPARTMENT IMPACT STATEMENT

ADMISSION/IN-PATIENT IMPACT:

In-Patients (#): Estimated Admission Duration (Days):

SPECIAL REQUIREMENTS (indicate need, or N/A):

Laboratory:

Radiology:

Nuclear Medicine:

Pharmacy:

Nursing Service:

Registrar:

Other Special Requirements:

APPROVALS:

PI's Department Head

Concurrence: _____
Name/Rank/Title

IMPACT SIGNATURES:

Name:
Rank:
Title:

Name:
Rank:
Title:

Name:
Rank:
Title:

Name:
Rank:
Title:

Name:
Rank:
Title:

Name:
Rank:
Title:

APPENDIX 7 (Page 1)
INVESTIGATOR'S ACKNOWLEDGMENT OF STANDARDS OF CONDUCT
AND/OR
CHANGE OF INVESTIGATOR REPORT

CIP#: _____ DATE: _____ ☐ NEW ☐ CHANGE

INVESTIGATORS: We, the investigators on the above-cited clinical investigation protocol, have read and understand the provisions of the following instructions and reports:

- 1. SECNAVINST 5370.2J, Standards of Conduct.
- 2 The Belmont Report, Ethical Principle and Guidelines for the Protection of Human Subjects of Research, 8 April 1979
- 3. SECNAVINST 3900.39B, Protection of Human Subjects

SECNAVINST 5370.2J is required reading for each investigator approved to conduct research in the Navy CIP. The Belmont Report and SECNAVINST 3900.39B must be reviewed if the protocol involves the use of human subjects.

<u>ACTION</u>	<u>ACTION</u>
ADD/DELETE/CHANGE (Circle One)	ADD/DELETE/CHANGE (Circle One)
PI/AI (Circle One)	PI/AI (Circle One)
NAME :	NAME:
GRADE: SSN:	GRADE: SSN:
PRD* (M/YR) :	PRD* (M/YR) :
STATUS**:	STATUS**:
DUTY STATION:	DUTY STATION:
DEPT:	DEPT:
% OF TIME:	% OF TIME:
SIGNATURE:	SIGNATURE:
DATE:	DATE:

APPENDIX 7 (Page 2)
INVESTIGATOR'S ACKNOWLEDGMENT OF STANDARDS OF CONDUCT
AND/OR
CHANGE OF INVESTIGATOR REPORT

AI ACTION	AI ACTION
ADD/DELETE/CHANGE (Circle One)	ADD/DELETE/CHANGE (Circle One)
NAME:	NAME:
GRADE: SSN:	GRADE: SSN:
PRD* (M/YR) :	PRD* (M/YR) :
STATUS**:	STATUS**;
DUTY STATION:	DUTY STATION:
DEPT: .	DEPT:
% OF TIME:	% OF TIME:
SIGNATURE:	SIGNATURE:
DATE:	DATE:
*PRD: Project rotation date (active duty personnel)	
**STATUS: Trainee (T), Staff (S), Civilian (C)	

A current curriculum vitae must be submitted for newly added investigators. Ensure that the version/revision date appears prominently on the document.

If there is a change in the PI, submit a new consent form with the name and telephone number of the new PI in the appropriate paragraphs. Ensure that the revision date appears on every page of the consent form(s).

If investigational agents are used, include a FDA Form 1571 or 1572 (or both, as applicable).

COMPLETED BY: _____
(PI's Signature)

Typed or Printed:

Name: _____
Grade: _____
Position: _____

APPENDIX 8 (Page 1)
SAMPLE INFORMED CONSENT DOCUMENT FOR
HUMAN USE RESEARCH PROPOSALS

The format of this sample Informed Consent Document for human use proposals appropriately addresses each of the required and additional elements, and corresponds to the sequence of statements in the checklist (APPENDIX 14).

CONSENT FOR VOLUNTARY PARTICIPATION IN A CLINICAL INVESTIGATION STUDY

Date: _____

1. I (name of participant), have been asked to voluntarily participate in a research project entitled, (CIP title and number) being conducted at (location)
2. The purpose of this research project is to (explain in detail).
3. My participation in this research project will be for a period of (duration of subject's participation).
4. The procedure for this project involves (describe all procedures, experimental and standard of care).
5. Specifically, I am aware that the experimental part of this research is (clearly distinguish experimental from standard of care procedures).
6. A total of (approximate number) subjects are expected to participate in this project.
7. The risks or discomforts that are possible are as follows (describe the foreseen risks). I accept these risks.
8. The research may/may not help me personally, and/but the results may help the investigator learn about (describe goal of CIP project) or aid in the treatment of other patients.
9. The alternate treatment, should I decline enrollment into this study, has been explained as follows:(describe alternate procedures).

Subject Initials and Date

APPENDIX 8 (Page 2)
SAMPLE INFORMED CONSENT DOCUMENT FOR
HUMAN USE RESEARCH PROPOSALS

or

This project is not designed to treat any medical condition that I may have; therefore, there is no alternative procedure or course of treatment that would be advantageous to me.

10. In all publications and presentations resulting from this research project, my anonymity is guaranteed; although, I realize that authorized Navy Medical Department personnel (and personnel from the Food and Drug Administration (FDA) only if applicable) may have access to my research file in order to verify that my rights have been safeguarded.

11. If I sustain any injury as a result of my participation in this study, my primary site of evaluation and treatment is at Naval Hospital (location). Although no compensation is available, my injury as a result of my participation will be evaluated and treated in keeping with the benefits or care to which I am entitled under applicable regulations.

12. If I have any questions regarding this research project, I may contact Dr. (name) at (telephone number). If I have any questions regarding my rights as an individual while participating in a clinical investigation project at Naval Hospital (location), I can contact the Clinical Investigation Department, at (phone number). If I believe I have been injured as a result of this project I may call the legal office at (telephone number).

13. My participation in this project is voluntary and that my refusal to participate will involve no penalty or loss of benefits to which I am entitled under applicable regulations. If I choose to participate, I am free to ask questions or to withdraw from the project at any time. If I should decide to withdraw from the research project, I will notify (name) at (telephone number) to ensure an orderly termination process. My withdrawal will involve no loss of benefits to which I am entitled.

Subject Initials and Date

APPENDIX 8 (Page 3)
SAMPLE INFORMED CONSENT DOCUMENT FOR
HUMAN USE RESEARCH PROPOSALS

When Appropriate One Or More Of The Following Elements Of
Consent Should Also Be Provided To Each Subject

- 14 I am aware that this study may involve risks to me (or to the embryo or fetus, if I become pregnant) which are currently unforeseeable. I am aware that I should promptly advise the investigator if I become pregnant or contemplate breast-feeding.
- 15 The investigator may terminate my participation in this project for the following reasons (list specific causes)
16. I have been informed that there will/will not be additional costs to me if I choose to participate in this project.
- 17 I may withdraw from this study at any time without prejudice to my future care. My withdrawal from this project will not cause me to lose any benefits to which I am otherwise entitled.
- 18 Any new significant finding developed during the course of the research, which may affect my willingness to participate further, will be explained to me.

I certify that I have received a copy of this consent form.

	_____ Subject's Signature/Date
	_____ Typed Name/Status/Sponsor's SSN
_____ Witness Signature/Date	_____ Investigator Signature/Date
_____ Witness Typed Name/Rank/SSN Name/Rank/SSN	_____ Investigator Typed

APPENDIX 8 (Page 4)
SAMPLE INFORMED CONSENT DOCUMENT FOR
HUMAN USE RESEARCH PROPOSALS

If Consent Form Is For Third Party Use,
Use This Signature Block:

I certify that I have received a copy of this consent form.

_____ Parent/Guardian Signature/Date	_____ Witness Signature/Date
_____ Parent/Guardian Typed Name	_____ Witness Typed Name/Rank/Title/SSN
_____ Subject Typed Name/Status/SSN	_____ Investigator Signature/Date
_____ Relationship to Patient/Subject Name/Rank/SSN	_____ Investigator Typed

N.B. EACH PAGE MUST BE NUMBERED AND HAVE SUBJECT'S (OR LEGAL
AUTHORITY'S) DATED INITIALS

APPENDIX 8 (Page 5)
SAMPLE INFORMED CONSENT DOCUMENT FOR
HUMAN USE RESEARCH PROPOSALS

PRIVACY ACT STATEMENT

1. Authority. 5 USC 301
- 2 Purpose. Medical research information will be collected to enhance basic medical knowledge, or to develop tests, procedures, and equipment to improve the diagnosis, treatment, or prevention of illness, injury or performance impairment.
- 3 Use. Medical research information will be used for statistical analysis and reports by the Departments of the Navy and Defense, and other U. S. Government agencies, provided this use is compatible with the purpose for which the information was collected. Use of the information may be granted to non-Government agencies or individuals by the Chief, Bureau of Medicine and Surgery in accordance with the provisions of the Freedom of Information Act.
4. Disclosure. I understand that all information contained in this Consent Statement or derived from the experiment described herein will be retained permanently at (name of performing activity) and salient portions thereof will be entered into my health record. I voluntarily agree to its disclosure to agencies or individuals identified in the preceding paragraph and I have been informed that failure to agree to such disclosure may negate the purposes for which the experiment was conducted.

SIGNATURES AND DATE SIGNED: PRINTED OR TYPED IDENTIFICATION:

_____ Subject/Date (if Applicable)	_____ Name/Status/Sponsor's SSN
_____ Parent/Guardian/Date (if Applicable)	_____ Name/Status/Sponsor's SSN
_____ Witness/Date	_____ Name/Grade or Rank/SSN

APPENDIX 9 (Page 1)
CONSENT FORM CHECK LIST

STUDY # _____
CPHS/IRB MEETING OF _____

Numbers 1 through 13B are required elements of informed consent for all research projects. The numbers on this check-list correspond to the paragraph numbers on the consent form sample.

<u>YES</u>	<u>NO</u>	<u>ARE THE FOLLOWING STATEMENTS PRESENT ON THE INFORMED CONSENT:</u>
_____	_____	1. A statement that the study involves research.
_____	_____	2. An explanation of the purpose of the research.
_____	_____	3. The expected duration of the subject's participation.
_____	_____	4. A description of the procedures to be followed.
_____	_____	5. Identification of the experimental procedures (if any) to be followed.
_____	_____	6. The approximate number of subjects involved in the study.
_____	_____	7. A description of any reasonably foreseen risks or discomforts to the subject.
_____	_____	8. A description of any benefits to the subject or to others which may reasonably be expected from the research.
_____	_____	9. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
_____	_____	10A. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
_____	_____	10B. If an investigational agent is used, a statement noting the possibility that the Food & Drug Administration may inspect the records.
_____	_____	11A. For research involving more than minimal risk, an explanation as to whether any compensation is available.
_____	_____	11B. An explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

APPENDIX 9 (Page 2)
CONSENT FORM CHECK LIST

<u>YES</u>	<u>NO</u>	
_____	_____	12. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights and whom to contact in the event of a research-related injury to the subject.
_____	_____	13A. A statement that participation is voluntary, and that refusal to participate will involve no loss of benefits to which the subject is otherwise entitled.
_____	_____	13B. A statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, one or more of the following elements of information shall also be provided to each subject:

_____	_____	14. A statement that the particular treatment or procedures may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable.
_____	_____	15. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
_____	_____	16. Any additional costs to the subject that may result from participation in the research.
_____	_____	17. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
_____	_____	18. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

APPENDIX 10 (Page 1)
POINTS TO CONSIDER
FOR PROTOCOLS USING HUMAN SUBJECTS

All protocols involving human subjects must address all of the following issues:

1 Describe the procedures to be used in the proposed study. Specify and explain the reasons for selecting the clinical conditions, sex, age, and other relevant characteristics (inclusion criteria) of individual subjects or population to be studied. Specify and explain the reasons for selecting the characteristics that disqualify potential subjects from the study (exclusion criteria). Specify and justify the number of subjects to be enrolled, the number of times observations will be made, and the interval(s) between observations. If medication is to be used, cite its proprietary and/or generic name, dose, route of administration, and name of person responsible for its administration. (If the indication, dose, or route of administration is inconsistent with the FDA approved label, does the proposed use constitute significantly increased risk to the subjects? Why or why not? Is an investigational new drug exemption application to the FDA required? Why or why not?) Describe in detail any discomfort, stresses, or aggravations of a chemical, physical, biological, psychological, or other nature which will be imposed. Cite your own or your associate investigator's experience with research of this kind.

2. Outline the possible benefit or advantage of the proposed study to the individual subject, group of subjects, and society.

3. Outline possible risks to subjects. An individual is considered to be "at risk" if exposed to the possibility of harm, physical, psychological, sociological, or other, as a consequence of any act or omission which increases the probability of harm inherent in the subject's daily life or in their occupation or their field of service. Document with appropriate references. Indicate procedures and safety measures that will be used to assess and reduce risks.

3a For greater than minimal risk studies, specify the name of the locally credentialed physician (or dentist in the case of a dental study) who has agreed to be responsible for medical monitoring with monitor's signature acknowledging the assignment. The appointment text should describe the phase of the study (e.g., recruitment, informed consent, data collection, data analysis or data storage) where subjects will be at

APPENDIX 10 (Page 2)
POINTS TO CONSIDER
FOR PROTOCOLS USING HUMAN SUBJECTS

greatest risk for harm, and consequently be the focus of attention for the medical monitor. Specify the monitor's duties. Suggest an appropriate frequency of on-site monitor attendance (i.e., every subject, every nth subject, etc.).

4. Explain the manner in which you will identify potential subjects, recruit them, and obtain their informed consent. (Are you planning to use clinical records or databases to identify potential subjects? Is this an invasion of privacy? Are you authorized to gain access to that data for the purpose of identifying potential subjects?) How will you minimize coercion? Include all recruiting posters and/or other intended advertisements. Describe the measures to be taken to protect the rights of privacy of the subjects. Attach copies of the consent and Privacy Act statements you intend to use.

5 What measures will be taken to enable the subject to omit specific procedures or to leave the study?

6 Indicate what changes you are likely to introduce during the course of the study, e.g., choice of subjects, obtaining informed consent, procedures to be employed, drugs, or other aspects of experimental design.

7. Describe the rationale for conducting the study on human subjects or populations and give reasons why this investigation could not be done with animal model(s). Summarize the nature and results of relevant studies done previously with animal models.

8. Describe the intent (or lack of intent) to share the results of the study with the subjects.

9 If applicable to the study's design, discuss the possibility that a placebo may constitute an unethical denial of an alternate study arm to placebo subjects. Specify criteria for breaking codes that blind investigators.

10 If this study proposes a population that requires third party consent (pediatric and/or adults not capable of providing their own consent), is the technical approach designed to provide an evident benefit to all enrolled subjects that would not ensue if they were not enrolled in this study?

APPENDIX 10 (Page 2)
POINTS TO CONSIDER
FOR PROTOCOLS USING HUMAN SUBJECTS

11 If this is a continuation of a project previously approved by a CPHS or IRB, indicate any changes in experimental design that may affect the risks or benefits to subjects. Summarize any untoward effects during the period since your application was last reviewed by a Committee. Attach copies of the updated consent and Privacy Act statements you intend to use.

APPENDIX 11 (Page 1)
ASSIGNING CIP NUMBERS TO RESEARCH PROPOSALS

CIDs will use the following system for assigning CIP numbers to proposals. **ELEVEN** criteria will be used to identify each research proposal. Each criteria is a letter except for number

1.

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
B	FY	L	0	0	0	0	0	0 Q		N S
P		H	H	A	I	R	V	L S		A T
S		S				B		G N		H R
						C		C P		x C
								E R		
								W		

1 Medical Facility (e.g., S = San Diego, CA; P = Portsmouth, VA; B = Bethesda, MD)

2. Two digit Fiscal Year

3. Approval Granting Authority (L = Local; H = NSHS; S=SECNAV)

4. Human Use Study (H = Human Study; 0 = No Human Subjects)

5. Animal Use Study (A = Animal Study; 0 = No Animals)

6. Investigational Agents (I = Investigational Agent; 0 = None)

7 Radioactive Materials or Biohazards (R = Radioactive Materials; B = Biohazardous Substances; C = Combined; 0 = None)

8. Retrovirology Study (V = Retrovirus Study; 0 = None)

9. National Oncology Group Studies: (0= None)
C = National Cancer Institute (NCI)
E = Eastern Cooperative Oncology Group (ECOG)
G = Gynecologic Oncology Group (GOG)
L = Cancer and Leukemia Group B (CALCG)
N = Northern California Oncology Group (NCOG)
P = Pediatric Oncology Group (POG)
Q =Children's Cancer Study Group (CCSG)
R = Radiation Therapy Oncology Group (RTOG)
S = National Surgical Adjuvant Breast & Bowel Project (NSABP)
W = Southwest Oncology Group (SWOG)

APPENDIX 11 (PAGE 2)
ASSIGNING CIP NUMBERS TO RESEARCH PROPOSALS

10. Sequential Number Series assigned by local CID, starting with 001 at the beginning of each new Fiscal Year.

11. Status of Proposal:
- | | |
|-------------------------|-----------------|
| N = New | S = Suspended |
| A = Approved/Continued | T = Terminated |
| H = Administrative Hold | R = Resubmitted |
| X = Completed | C = Change |

APPENDIX 12 (Page 1)
CLINICAL INVESTIGATION PERIODIC REVIEW

CIP#: _____

1. DATE OF THIS REVIEW: _____

2. DATE OF PREVIOUS REVIEW: _____

3. PI: _____

4. TITLE: _____

5. LOCATION OF STUDY: _____

6. NAMES OF AIs:

AI: _____

AI: _____

AI: _____

AI: _____

AI: _____

AI: _____

7. DATE PROTOCOL RECEIVED INITIAL CPHS/IRB APPROVAL: _____

DATE PROTOCOL INITIATED: _____

8. FOR ANIMAL USE STUDIES: Attach a copy of the most current periodic review or periodic report required or prepared by your local IACUC or by MED-WE.

FOR HUMAN USE STUDIES: Provide an attachment listing SSNs, initials and enrollment dates of all subjects enrolled in the study.

9. PROGRESS DURING THIS REPORTING PERIOD: Provide an attachment that provides the information requested in items a. - d. (below):

a. Briefly describe the most salient accomplishments.

b. List the manuscripts submitted for publication since the last periodic report. Note those that have been accepted for publication, with publication date if available. List by author(s), title, journal (book, editor(s), publisher), volume number, page number(s), and date.

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CLINICAL INVESTIGATION PERIODIC REVIEW

c. List other material(s) (e.g., abstracts) that have been submitted for publication during the last year. Note those that have been accepted for publication, with publication date if available. List author(s), title, society, place of meeting, and date.

d List presentations made during the last year (National, International, Local Societies, Military Meetings, etc.). Use asterisk (*) if the presentation was associated with a manuscript.

e. Specify all untoward events and document them with attached copies of incident reports and/or Investigational Agent Status Reports (if relevant).

10. If an unforeseen delay in the conduct of the study has occurred, attach a detailed explanation.

(Signature, Principal Investigator) (Date)

.....

RECOMMENDATION BY CPHS/IRB, NAVAL MEDICAL CENTER _____
(Location)

Documented on CPHS/IRB minutes dated: _____

- | | |
|--|-------------------------------------|
| <input type="checkbox"/> APPROVED FOR CONTINUATION | <input type="checkbox"/> COMPLETED |
| <input type="checkbox"/> REINSTATED FOR CONTINUATION | <input type="checkbox"/> SUSPENDED |
| DATE OF NEXT CONTINUING REVIEW _____ | <input type="checkbox"/> TERMINATED |
| (Day/Mo/Yr) | |

(Signature, Chair, CPHS/IRB) (Date)

.....

ACTION BY COMMANDER, NAVAL MEDICAL CENTER _____
(Location)

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CLINICAL INVESTAGATION PERIODIC REVIEW

☐ MINUTES APPROVED AS SUBMITTED

☐ CO NON-CONCURRENCE, DIRECTED

THAT _____

Recorded

by: _____
(Head, CID) (Date) _____.